

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 307/20, A61K 31/34, 31/66, 31/665, 31/70, 31/16, C07D 405/12, C07C 311/18, C07H 15/18, C07F 9/655, 9/6584		A1	(11) International Publication Number: WO 99/33815 (43) International Publication Date: 8 July 1999 (08.07.99)
(21) International Application Number: PCT/US98/04595 (22) International Filing Date: 9 March 1998 (09.03.98)		Bonham Court, Durham, NC 27703 (US). KAZMIERSKI, Wieslaw, Wieczyslaw [US/US]; 1221 Stone Creek Way, Raleigh, NC 27615 (US). SPALTENSTEIN, Andrew [US/US]; 4105 Brester Drive, Raleigh, NC 27606 (US).	
(30) Priority Data: 08/998,050 24 December 1997 (24.12.97) US		(74) Agents: HALEY, James, F., Jr.; Fish & Neave, 1251 Avenue of the Americas, New York, NY 10020 (US) et al.	
(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application US 08/998,050 (CIP) Filed on 24 December 1997 (24.12.97)		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).	
(71) Applicant (for all designated States except US): VERTEX PHARMACEUTICALS INCORPORATED [US/US]; 130 Waverly Street, Cambridge, MA 02139-4242 (US).		Published With international search report.	
(72) Inventors; and (75) Inventors/Applicants (for US only): TUNG, Roger, D. [US/US]; 54 Richfield Road, Arlington, MA 01274 (US). HALE, Michael, R. [US/US]; 42 Sunset Road, Bedford, MA 01730 (US). BAKER, Christopher, T. [US/US]; Apartment 5, 23 Judith Lane, Waltham, MA 02154 (US). FURFINE, Eric, Steven [US/US]; 4133 Livingstone Place, Durham, NC 27707 (US). KALDOR, Istvan [US/US]; 7		(54) Title: SULPHONAMIDE DERIVATIVES AS PRODRUGS OF ASPARTYL PROTEASE INHIBITORS (57) Abstract	
<p>The present invention relates to prodrugs of a class of sulfonamides which are aspartyl protease inhibitors. In one embodiment, this invention relates to a novel class of prodrugs of HIV aspartyl protease inhibitors characterized by favorable aqueous solubility, high oral bioavailability and facile <i>in vivo</i> generation of the active ingredient. This invention also relates to pharmaceutical compositions comprising these prodrugs. The prodrugs and pharmaceutical compositions of this invention are particularly well suited for decreasing the pill burden and increasing patient compliance. This invention also relates to methods of treating mammals with these prodrugs and pharmaceutical compositions.</p>			

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LJ	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		

SULPHONAMIDE DERIVATIVES AS PRODRUGS OF ASPARTYL PROTEASE INHIBITORS

TECHNICAL FIELD OF THE INVENTION

The present invention relates to prodrugs of a
5 class of sulfonamides which are aspartyl protease
inhibitors. In one embodiment, this invention relates to
a novel class of prodrugs of HIV aspartyl protease
inhibitors characterized by favorable aqueous solubility,
high oral bioavailability and facile *in vivo* generation
10 of the active ingredient. This invention also relates to
pharmaceutical compositions comprising these prodrugs.
The prodrugs and pharmaceutical compositions of this
invention are particularly well suited for decreasing the
pill burden and increasing patient compliance. This
15 invention also relates to methods of treating mammals
with these prodrugs and pharmaceutical compositions.

BACKGROUND OF THE INVENTION

Aspartyl protease inhibitors are considered the
most effective current drug in the fight against HIV
20 infection. These inhibitors, however, require certain
physicochemical properties in order to achieve good
potency against the enzyme. One of these properties is
high hydrophobicity. Unfortunately, this property
results in poor aqueous solubility and low oral
25 bioavailability.

United States Patent 5,585,397 describes a
class of sulfonamide compounds that are inhibitors of the
aspartyl protease enzyme. These compounds illustrate the

drawbacks concomitant to pharmaceutical compositions comprising hydrophobic aspartyl protease inhibitors. For example, VX-478 (4-amino-N-((2-syn,3S)-2-hydroxy-4-phenyl-2((S)-tetrahydrofuran-3-yl-oxy carbonylamino)-butyl-N-isobutyl-benzenesulfonamide) is an aspartyl protease inhibitor disclosed in the '397 patent. It has a relatively low aqueous solubility. While the oral bioavailability of this inhibitor in a "solution" formulation is excellent, the dosage of VX-478 in this form is severely limited by the amount of liquid present in the particular liquid dosage form, e.g., encapsulated into a soft gelatin capsule. A higher aqueous solubility would increase drug load per unit dosage of VX-478.

Currently, the solution formulation of VX-478 produces an upper limit of 150 mg of VX-478 in each capsule. Given a therapeutic dose of 2400 mg/day of VX-478, this formulation would require a patient to consume 16 capsules per day. Such a high pill burden would likely result in poor patient compliance, thus producing sub-optimal therapeutic benefit of the drug. The high pill burden is also a deterrent to increasing the amount of the drug administered per day to a patient. Another drawback of the pill burden and the concomitant patient compliance problem is in the treatment of children infected with HIV.

Furthermore, these "solution" formulations, such as the mesylate formulation, are at a saturation solubility of VX-478. This creates the real potential of having the drug crystallize out of solution under various storage and/or shipping conditions. This, in turn, would likely result in a loss of some of the oral bioavailability achieved with VX-478.

One way of overcoming these problems is to develop a standard solid dosage form, such as a tablet or a capsule or a suspension form. Unfortunately, such solid dosage forms have much lower oral bioavailability
5 of the drug.

Thus, there is a need to improve the drug load per unit dosage form for aspartyl protease inhibitors. Such an improved dosage form would reduce the pill burden and increase patient compliance. It would also provide
10 for the possibility of increasing the amounts of the drug administered per day to a patient.

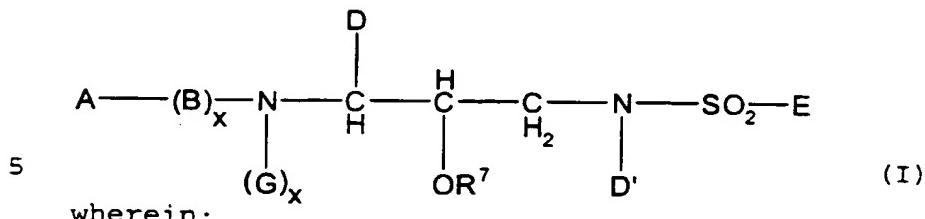
SUMMARY OF THE INVENTION

The present invention provides novel prodrugs of a class of sulfonamide compounds that are inhibitors
15 of aspartyl protease, in particular, HIV aspartyl protease. These prodrugs are characterized by excellent aqueous solubility, increased bioavailability and are readily metabolized into the active inhibitors *in vivo*. The present invention also provides pharmaceutical
20 compositions comprising these prodrugs and methods of treating HIV infection in mammals using these prodrugs and the pharmaceutical compositions thereof.

These prodrugs can be used alone or in combination with other therapeutic or prophylactic
25 agents, such as anti-virals, antibiotics, immunomodulators or vaccines, for the treatment or prophylaxis of viral infection.

It is a principal object of this invention to provide a novel class of prodrugs of sulfonamide
30 compounds that are aspartyl protease inhibitors, and

particularly, HIV aspartyl protease inhibitors. This novel class of sulfonamides is represented by formula I:



- 5 A is selected from H; Ht; -R¹-Ht; -R¹-C₁-C₆ alkyl, which is optionally substituted with one or more groups independently selected from hydroxy, C₁-C₄ alkoxy, Ht, -O-Ht, -NR²-CO-N(R²)₂ or -CO-N(R²)₂;
- 10 -R¹-C₂-C₆ alkenyl, which is optionally substituted with one or more groups independently selected from hydroxy, C₁-C₄ alkoxy, Ht, -O-Ht, -NR²-CO-N(R²)₂ or -CO-N(R²)₂; or R⁷;
- 15 each R¹ is independently selected from -C(O)-, -S(O)₂-, -C(O)-C(O)-, -O-C(O)-, -O-S(O)₂, -NR²-S(O)₂-, -NR²-C(O)- or -NR²-C(O)-C(O)-;
- 20 each Ht is independently selected from C₃-C₇ cycloalkyl; C₅-C₇ cycloalkenyl; C₆-C₁₀ aryl; or a 5-7 membered saturated or unsaturated heterocycle, containing one or more heteroatoms selected from N, N(R²), O, S and S(O)_n; wherein said aryl or said heterocycle is optionally fused to Q; and wherein any member of said Ht is optionally substituted with one or more substituents
- 25 independently selected from oxo, -OR², SR², -R², -N(R²)(R²), -R²-OH, -CN, -CO₂R², -C(O)-N(R²)₂, -S(O)₂-N(R²)₂, -N(R²)-C(O)-R², -C(O)-R², -S(O)_n-R², -OCF₃, -S(O)_n-Q, methylenedioxy, -N(R²)-S(O)₂(R²), halo, -CF₃, -NO₂, Q, -OQ, -OR⁷, -SR⁷, -R⁷, -N(R²)(R⁷) or -N(R⁷)₂;
- 30 each R² is independently selected from H, or C₁-C₄ alkyl optionally substituted with Q;

B, when present, is $-N(R^2)-C(R^3)_2-C(O)-$;
each x is independently 0 or 1;
each R³ is independently selected from H, Ht,
C₁-C₆ alkyl, C₂-C₆ alkenyl, C₃-C₆ cycloalkyl or C₅-C₆
5 cycloalkenyl; wherein any member of said R³, except H, is
optionally substituted with one or more substituents
selected from -OR², -C(O)-NH-R², -S(O)_n-N(R²)(R²), Ht,
-CN, -SR², -CO₂R², NR²-C(O)-R²;
each n is independently 1 or 2;

10 G, when present, is selected from H, R⁷ or C₁-C₄
alkyl, or, when G is C₁-C₄ alkyl, G and R⁷ are bound to one
another either directly or through a C₁-C₃ linker to form
a heterocyclic ring; or
when G is not present (i.e., when x in (G)_x is
15 0), then the nitrogen to which G is attached is bound
directly to the R⁷ group on -OR⁷;

D and D' are independently selected from Q; C₁-
C₆ alkyl, which is optionally substituted with one or more
groups selected from C₃-C₆ cycloalkyl, -OR², -R³,
20 -O-Q or Q; C₂-C₄ alkenyl, which is optionally substituted
with one or more groups selected from C₃-C₆ cycloalkyl, -
OR², -R³, -O-Q or Q; C₃-C₆ cycloalkyl, which is optionally
substituted with or fused to Q; or C₅-C₆ cycloalkenyl,
which is optionally substituted with or fused to Q;

25 each Q is independently selected from a 3-7
membered saturated, partially saturated or unsaturated
carbocyclic ring system; or a 5-7 membered saturated,
partially saturated or unsaturated heterocyclic ring
containing one or more heteroatoms selected from O, N, S,
30 S(O)_n or N(R²); wherein Q is optionally substituted with
one or more groups selected from oxo, -OR², -R², -N(R²)₂,
-N(R²)-C(O)-R², -R²-OH, -CN, -CO₂R²,

$-C(O)-N(R^2)_2$, halo or $-CF_3$;

E is selected from Ht; O-Ht; Ht-Ht; $-O-R^3$;

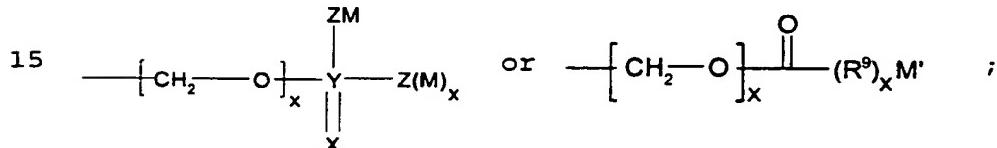
$-N(R^2)(R^3)$; C_1-C_6 alkyl, which is optionally substituted with one or more groups selected from R^4 or Ht; C_2-C_6

5 alkenyl, which is optionally substituted with one or more groups selected from R^4 or Ht; C_3-C_6 saturated carbocycle, which is optionally substituted with one or more groups selected from R^4 or Ht; or C_5-C_6 unsaturated carbocycle, which is optionally substituted with one or more groups

10 selected from R^4 or Ht;

each R^4 is independently selected from $-OR^2$, $-SR^2$, $-C(O)-NHR^2$, $-S(O)_2-NHR^2$, halo, $-NR^2-C(O)-R^2$, $-N(R^2)_2$ or $-CN$;

each R^7 is independently selected from



wherein each M is independently selected

from H, Li, Na, K, Mg, Ca, Ba, $-N(R^2)_4$, C_1-C_{12} -alkyl, C_2-C_{12} -alkenyl, or $-R^6$; wherein 1 to 4 $-CH_2$ radicals of the alkyl or alkenyl group, other than the $-CH_2$ that is bound

20 to Z, is optionally replaced by a heteroatom group selected from O, S, $S(O)$, $S(O_2)$, or $N(R^2)$; and wherein any hydrogen in said alkyl, alkenyl or R^6 is optionally replaced with a substituent selected from oxo, $-OR^2$, $-R^2$, $N(R^2)_2$, $N(R^2)_3$, R^2OH , $-CN$, $-CO_2R^2$, $-C(O)-N(R^2)_2$, $S(O)_2-$

25 $N(R^2)_2$, $N(R^2)-C(O)-R_2$, $C(O)R^2$, $-S(O)_n-R^2$, OCF_3 , $-S(O)_n-R^6$, $N(R^2)-S(O)_2(R^2)$, halo, $-CF_3$, or $-NO_2$;

M' is H, C_1-C_{12} -alkyl, C_2-C_{12} -alkenyl, or $-R^6$;

wherein 1 to 4 $-CH_2$ radicals of the alkyl or alkenyl group is optionally replaced by a heteroatom group selected

30 from O, S, $S(O)$, $S(O_2)$, or $N(R^2)$; and wherein any hydrogen

in said alkyl, alkenyl or R⁶ is optionally replaced with a substituent selected from oxo, -OR², -R², -N(R²)₂, N(R²)₃, -R²OH, -CN, -CO₂R², -C(O)-N(R²)₂, -S(O)₂-N(R²)₂, -N(R²)-C(O)-R₂, -C(O)R², -S(O)_n-R², -OCF₃, -S(O)_n-R⁶, 5 -N(R²)-S(O)₂(R²), halo, -CF₃, or -NO₂;

Z is CH₂, O, S, N(R²)₂, or, when M is absent, H;

Y is P or S;

X is O or S; and

R⁹ is C(R²)₂, O or N(R²); and wherein when Y is

10 S, Z is not S; and

R⁶ is a 5-6 membered saturated, partially saturated or unsaturated carbocyclic or heterocyclic ring system, or an 8-10 membered saturated, partially saturated or unsaturated bicyclic ring system; wherein 15 any of said heterocyclic ring systems contains one or more heteroatoms selected from O, N, S, S(O)_n or N(R²); and wherein any of said ring systems optionally contains 1 to 4 substituents independently selected from OH, C₁-C₄ alkyl, O-C₁-C₄ alkyl or OC(O)C₁-C₄ alkyl.

20 It is also an object of this invention to provide pharmaceutical compositions comprising the sulfonamide prodrugs of formula I and methods for their use as prodrugs of HIV aspartyl protease inhibitors.

DETAILED DESCRIPTION OF THE INVENTION

25 In order that the invention herein described may be more fully understood, the following detailed description is set forth. In the description, the following abbreviations are used:

	<u>Designation</u>	<u>Reagent or Fragment</u>
30	Ac	acetyl
	Me	methyl
	Et	ethyl

	Bzl	benzyl
	Trityl	triphenylmethyl
	Asn	D- or L-asparagine
	Ile	D- or L-isoleucine
5	Phe	D- or L-phenylalanine
	Val	D- or L-valine
	Boc	tert-butoxycarbonyl
	Cbz	benzyloxycarbonyl (carbobenzyloxy)
	Fmoc	9-fluorenylmethoxycarbonyl
10	DCC	dicyclohexylcarbodiimide
	DIC	diisopropylcarbodiimide
	EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
	HOEt	1-hydroxybenzotriazole
15	HOSu	1-hydroxysuccinimide
	TFA	trifluoroacetic acid
	DIEA	diisopropylethylamine
	DBU	1,8-diazabicyclo(5.4.0)undec-7-ene
	EtOAc	ethyl acetate
20	The following terms are employed herein:	
	Unless expressly stated to the contrary, the terms "-SO ₂ - " and "-S(O) ₂ - " as used herein refer to a sulfone or sulfone derivative (i.e., both appended groups linked to the S), and not a sulfinate ester.	
25	For the compounds of formula I, and intermediates thereof, the stereochemistry of OR ⁷ is defined relative to D on the adjacent carbon atom, when the molecule is drawn in an extended zig-zag representation (such as that drawn for compounds of	
30	formula XI, XV, XXII, XXIII and XXXI). If both OR ⁷ and D reside on the same side of the plane defined by the extended backbone of the compound, the stereochemistry of	

OR⁷ will be referred to as "syn". If OR⁷ and D reside on opposite sides of that plane, the stereochemistry of OR⁷ will be referred to as "anti".

5 The term "aryl", alone or in combination with any other term, refers to a carbocyclic aromatic radical containing the specified number of carbon atoms.

The term "heterocyclic" refers to a stable 5-7 membered monocycle or 8-11 membered bicyclic heterocycle which is either saturated or unsaturated, and which may 10 be optionally benzofused if monocyclic. Each heterocycle consists of carbon atoms and from one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur. As used herein, the terms "nitrogen and 15 sulfur heteroatoms" include any oxidized form of nitrogen and sulfur, and the quaternized form of any basic nitrogen. The heterocyclic ring may be attached by any heteroatom of the cycle which results in the creation of a stable structure. Preferred heterocycles defined above include, for example, benzimidazolyl, imidazolyl, 20 imidazolinoyl, imidazolidinyl, quinolyl, isoquinolyl, indolyl, pyridyl, pyrrolyl, pyrrolinyl, pyrazolyl, pyrazinyl, quinoxolyl, piperidinyl, morpholinyl, thiamorpholinyl, furyl, thienyl, triazolyl, thiazolyl, β -carbolinyl, tetrazolyl, thiazolidinyl, benzofuranoyl, 25 thiamorpholinyl sulfone, benzoxazolyl, oxopiperidinyl, oxopyrroldinyl, oxoazepinyl, azepinyl, isoxazolyl, tetrahydropyranyl, tetrahydrofuranyl, thiadiazoyl, benzodioxolyl, thiophenyl, tetrahydrothiophenyl and sulfolanyl.

30 The terms "HIV protease" and "HIV aspartyl protease" are used interchangeably and refer to the aspartyl protease encoded by the human immunodeficiency

virus type 1 or 2. In a preferred embodiment of this invention, these terms refer to the human immunodeficiency virus type 1 aspartyl protease.

The term "pharmaceutically effective amount" 5 refers to an amount effective in treating HIV infection in a patient. The term "prophylactically effective amount" refers to an amount effective in preventing HIV infection in a patient. As used herein, the term "patient" refers to a mammal, including a human.

10 The term "pharmaceutically acceptable carrier or adjuvant" refers to a non-toxic carrier or adjuvant that may be administered to a patient, together with a compound of this invention, and which does not destroy the pharmacological activity thereof.

15 Pharmaceutically acceptable salts of the compounds of this invention include those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acids include hydrochloric, hydrobromic, sulfuric, nitric, perchloric, 20 fumaric, maleic, phosphoric, glycollic, lactic, salicylic, succinic, toluene-p-sulfonic, tartaric, acetic, citric, methanesulfonic, formic, benzoic, malonic, naphthalene-2-sulfonic and benzenesulfonic acids. Other acids, such as oxalic, while not in 25 themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts.

Salts derived from appropriate bases include 30 alkali metal (e.g., sodium), alkaline earth metal (e.g., magnesium), ammonium and N-(C₁₋₄ alkyl)⁴⁺ salts.

The term "thiocarbamates" refers to compounds containing the functional group N-SO₂-O.

The compounds of this invention contain one or more asymmetric carbon atoms and thus occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. All such isomeric forms of these compounds are expressly included in the present invention. Each stereogenic carbon may be of the R or S configuration. The explicitly shown hydroxyl is also preferred to be syn to D, in the extended zigzag conformation between the nitrogens shown in compounds of formula I.

Combinations of substituents and variables envisioned by this invention are only those that result in the formation of stable compounds. The term "stable", as used herein, refers to compounds which possess stability sufficient to allow manufacture and administration to a mammal by methods known in the art. Typically, such compounds are stable at a temperature of 40°C or less, in the absence of moisture or other chemically reactive conditions, for at least a week.

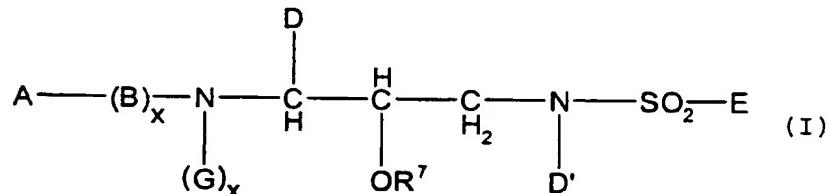
The compounds of the present invention may be used in the form of salts derived from inorganic or organic acids. Included among such acid salts, for example, are the following: acetate, adipate, alginic acid, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-

naphthalenesulfonate, nicotinate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate and undecanoate.

5 This invention also envisions the quaternization of any basic nitrogen-containing groups of the compounds disclosed herein. The basic nitrogen can be quaternized with any agents known to those of ordinary skill in the art including, for example, lower alkyl
 10 halides, such as methyl, ethyl, propyl and butyl chloride, bromides and iodides; dialkyl sulfates including dimethyl, diethyl, dibutyl and diamyl sulfates; long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides; and aralkyl
 15 halides including benzyl and phenethyl bromides. Water or oil-soluble or dispersible products may be obtained by such quaternization.

The novel sulfonamides of this invention are those of formula I:

20



wherein:

25 A is selected from H; Ht; $-R^1-Ht$; $-R^1-C_1-C_6$ alkyl, which is optionally substituted with one or more groups independently selected from hydroxy, C_1-C_4 alkoxy, Ht, $-O-Ht$, $-NR^2-CO-N(R^2)_2$ or $-CO-N(R^2)_2$; $-R^1-C_2-C_6$ alkenyl, which is optionally substituted with
 30 one or more groups independently selected from hydroxy, C_1-C_4 alkoxy, Ht, $-O-Ht$, $-NR^2-CO-N(R^2)_2$ or $-CO-N(R^2)_2$; or R' ;

each R¹ is independently selected from -C(O)-, -S(O)₂-, -C(O)-C(O)-, -O-C(O)-, -O-S(O)₂, -NR²-S(O)₂-, -NR²-C(O)- or -NR²-C(O)-C(O)-;

each Ht is independently selected from C₃-C₇ cycloalkyl; C₅-C₇ cycloalkenyl; C₆-C₁₀ aryl; or a 5-7 membered saturated or unsaturated heterocycle, containing one or more heteroatoms selected from N, N(R²), O, S and S(O)_n; wherein said aryl or said heterocycle is optionally fused to Q; and wherein any member of said Ht is

optionally substituted with one or more substituents independently selected from oxo, -OR², SR², -R², -N(R²)(R²), -R²-OH, -CN, -CO₂R², -C(O)-N(R²)₂, -S(O)₂-N(R²)₂, -N(R²)-C(O)-R², -C(O)-R², -S(O)_n-R², -OCF₃, -S(O)_n-Q, methylenedioxy, -N(R²)-S(O)₂(R²), halo, -CF₃, -NO₂, Q, -OQ, -OR⁷, -SR⁷, -R⁷, -N(R²)(R⁷) or -N(R⁷)₂;

each R² is independently selected from H, or C₁-C₄ alkyl optionally substituted with Q;

B, when present, is -N(R²)-C(R³)₂-C(O)-;

each x is independently 0 or 1;

each R³ is independently selected from H, Ht, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₃-C₆ cycloalkyl or C₅-C₆ cycloalkenyl; wherein any member of said R³, except H, is optionally substituted with one or more substituents selected from -OR², -C(O)-NH-R², -S(O)_n-N(R²)(R²), Ht, -CN, -SR², -CO₂R², NR²-C(O)-R²;

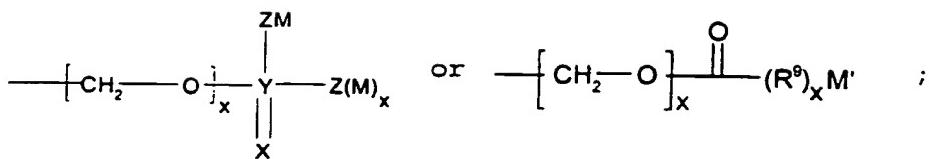
each n is independently 1 or 2;

G, when present, is selected from H, R⁷ or C₁-C₄ alkyl, or, when G is C₁-C₄ alkyl, G and R⁷ are bound to one another either directly or through a C₁-C₃ linker to form a heterocyclic ring; or

when G is not present (i.e., when x in (G)_x is 0), then the nitrogen to which G is attached is bound

directly to the R⁷ group in -OR⁷ with the concomitant displacement of one -ZM group from R⁷;

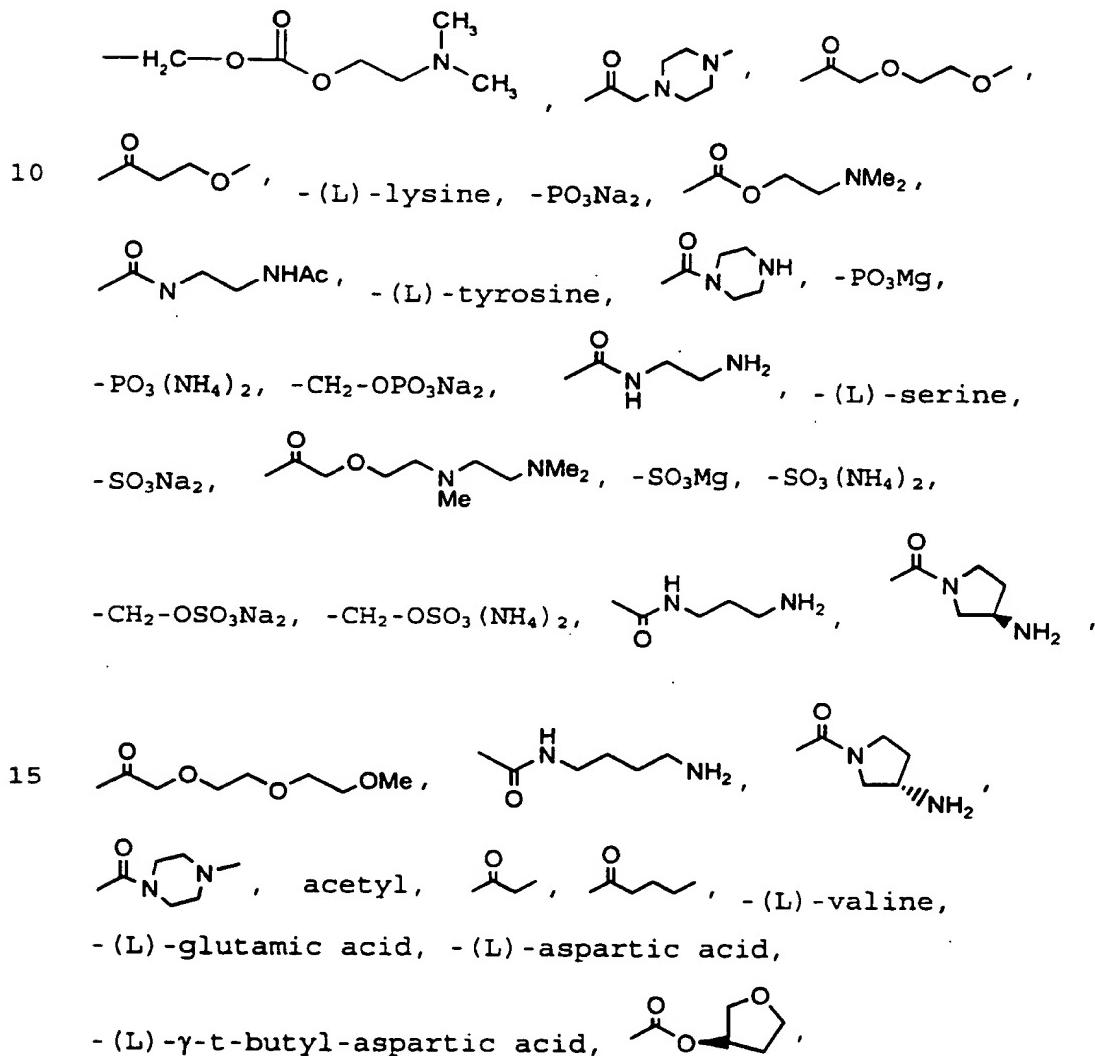
- D and D' are independently selected from Q; C₁-C₆ alkyl, which is optionally substituted with one or more groups selected from C₃-C₆ cycloalkyl, -OR², -R³, -O-Q or Q; C₂-C₄ alkenyl, which is optionally substituted with one or more groups selected from C₃-C₆ cycloalkyl, -OR², -R³, -O-Q or Q; C₃-C₆ cycloalkyl, which is optionally substituted with or fused to Q; or C₅-C₆ cycloalkenyl, which is optionally substituted with or fused to Q;
- each Q is independently selected from a 3-7 membered saturated, partially saturated or unsaturated carbocyclic ring system; or a 5-7 membered saturated, partially saturated or unsaturated heterocyclic ring containing one or more heteroatoms selected from O, N, S, S(O)_n or N(R²); wherein Q is optionally substituted with one or more groups selected from oxo, -OR², -R², -N(R²)₂, -N(R²)-C(O)-R², -R²-OH, -CN, -CO₂R², -C(O)-N(R²)₂, halo or -CF₃;
- E is selected from Ht; O-Ht; Ht-Ht; -O-R³; -N(R²)(R³); C₁-C₆ alkyl, which is optionally substituted with one or more groups selected from R⁴ or Ht; C₂-C₆ alkenyl, which is optionally substituted with one or more groups selected from R⁴ or Ht; C₃-C₆ saturated carbocycle, which is optionally substituted with one or more groups selected from R⁴ or Ht;
- each R⁴ is independently selected from -OR², -SR², -C(O)-NHR², -S(O)₂-NHR², halo, -NR²-C(O)-R², -N(R²)₂ or -CN;
- each R⁷ is independently selected from



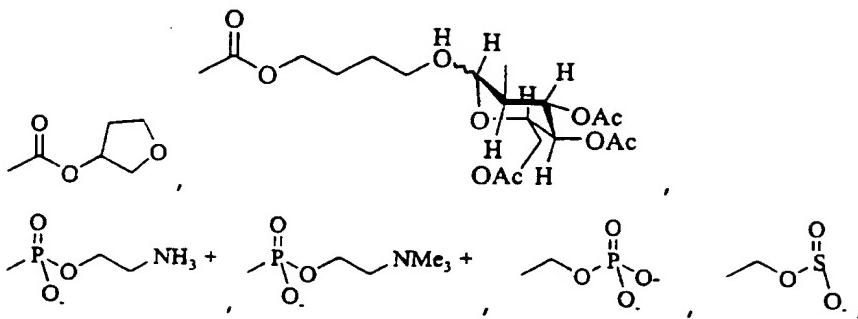
- wherein each M is independently selected from H, Li, Na, K, Mg, Ca, Ba, $\text{-N(R}^2\text{)}_4$, $\text{C}_1\text{-C}_{12}\text{-alkyl}$, $\text{C}_2\text{-C}_{12}\text{-alkenyl}$, or -R^6 ; wherein 1 to 4 $-\text{CH}_2$ radicals of the alkyl or alkenyl group, other than the $-\text{CH}_2$ that is bound to Z, is optionally replaced by a heteroatom group selected from O, S, S(O) , $\text{S(O}_2\text{)}$, or $\text{N(R}^2\text{)}$; and wherein any hydrogen in said alkyl, alkenyl or R^6 is optionally replaced with a substituent selected from oxo, $-\text{OR}^2$, $-\text{R}^2$, $\text{N(R}^2\text{)}_2$, $\text{N(R}^2\text{)}_3$, R^2OH , $-\text{CN}$, $-\text{CO}_2\text{R}^2$, $-\text{C(O)-N(R}^2\text{)}_2$, $\text{S(O)}_2\text{-N(R}^2\text{)}_2$, $\text{N(R}^2\text{)}\text{-C(O)-R}_2$, C(O)R^2 , $-\text{S(O)}_n\text{-R}^2$, $-\text{OCF}_3$, $-\text{S(O)}_n\text{-R}^6$, $\text{N(R}^2\text{)}\text{-S(O)}_2\text{(R}^2\text{)}$, halo, $-\text{CF}_3$, or $-\text{NO}_2$;
- M' is H, $\text{C}_1\text{-C}_{12}\text{-alkyl}$, $\text{C}_2\text{-C}_{12}\text{-alkenyl}$, or -R^6 ;
- wherein 1 to 4 $-\text{CH}_2$ radicals of the alkyl or alkenyl group is optionally replaced by a heteroatom group selected from O, S, S(O) , $\text{S(O}_2\text{)}$, or $\text{N(R}^2\text{)}$; and wherein any hydrogen in said alkyl, alkenyl or R^6 is optionally replaced with a substituent selected from oxo, $-\text{OR}^2$, $-\text{R}^2$, $-\text{N(R}^2\text{)}_2$, $\text{N(R}^2\text{)}_3$, $-\text{R}^2\text{OH}$, $-\text{CN}$, $-\text{CO}_2\text{R}^2$, $-\text{C(O)-N(R}^2\text{)}_2$, $-\text{S(O)}_2\text{-N(R}^2\text{)}_2$, $-\text{N(R}^2\text{)}\text{-C(O)-R}_2$, $-\text{C(O)R}^2$, $-\text{S(O)}_n\text{-R}^2$, $-\text{OCF}_3$, $-\text{S(O)}_n\text{-R}^6$, $-\text{N(R}^2\text{)}\text{-S(O)}_2\text{(R}^2\text{)}$, halo, $-\text{CF}_3$, or $-\text{NO}_2$;
- Z is CH_2 , O, S, $\text{N(R}^2\text{)}_2$, or, when M is not present, H.
- Y is P or S;
- X is O or S; and
- R^9 is $\text{C(R}^2\text{)}_2$, O or $\text{N(R}^2\text{)}$; and wherein when Y is S, Z is not S; and
- R^6 is a 5-6 membered saturated, partially saturated or unsaturated carbocyclic or heterocyclic ring

system, or an 8-10 membered saturated, partially saturated or unsaturated bicyclic ring system; wherein any of said heterocyclic ring systems contains one or more heteroatoms selected from O, N, S, S(O)_n or N(R²); and wherein any of said ring systems optionally contains 1 to 4 substituents independently selected from OH, C₁-C₄ alkyl, O-C₁-C₄ alkyl or O-C(O)-C₁-C₄ alkyl.

Preferably, at least one R' is selected from:



- (L) - (L) - 3-pyridylalanine, - (L) - histidine, -CHO, $\text{C}(=\text{O})\text{CF}_3$,



5 PO_3K_2 , PO_3Ca , PO_3 -spermamine, PO_3 -(spermidine)₂ or
PO₃-(meglamine)₂.

10 It will be understood by those of skill in the art that component M or M' in the formulae set forth herein will have either a covalent, a covalent/zwitterionic, or an ionic association with either Z or R⁹ depending upon the actual choice for M or M'. When M or M' is hydrogen, alkyl, alkenyl, or R⁶, M or M' is covalently bound to R⁹ or Z. If M is a mono- or bivalent metal or other charged species (i.e., NH₄⁺), there is an ionic interaction between M and Z and the resulting compound is a salt.

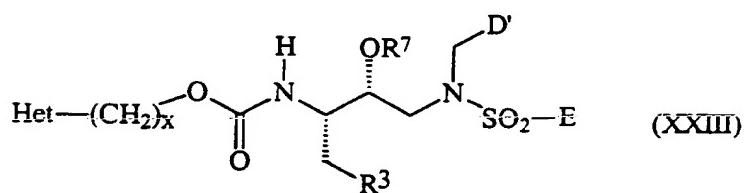
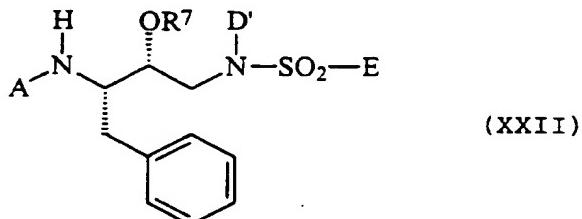
15 When x is 0 in (M)_x, Z may be a charged species. When that occurs, the other M may be oppositely charged to produce a 0 net charge on the molecule.

20 Alternatively, the counter ion may located elsewhere in the molecule.

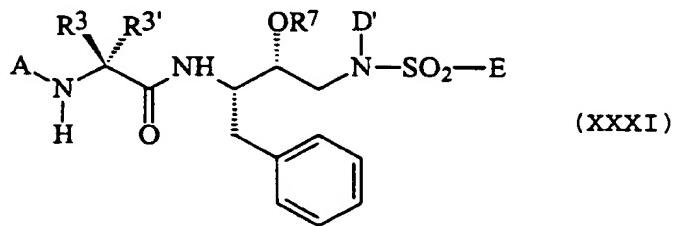
25 Except where expressly provided to the contrary, as used herein, the definitions of variables A, R¹-R⁴, R⁶-R⁹, Ht, B, x, n, D, D', M, Q, X, Y, Z and E are to be taken as they are defined above for the compounds of formula I.

According to a preferred embodiment, the compounds of this invention are those represented by formulas XXII, XXIII or XXXI:

5



10



wherein A, R³, R⁷, Ht, D, D', x, E are as defined above
15 for compounds of formula I. For ease of reference, the two R³ moieties present in formula XXXI have been labeled R³ and R^{3'}.

For compounds of formula XXII, more preferred compounds are those wherein:

20 A is selected from 3-tetrahydrofuryl-O-C(O)-, 3-(1,5-dioxane)-O-C(O)-, or 3-hydroxy-hexahydrofura[2,3-b]-furanyl-O-C(O)-;

D' is C₁-C₄ alkyl which is optionally substituted with one or more groups selected from the group consisting of C₃-C₆ cycloalkyl, -OR², -R³, -O-Q and Q;

E is C₆-C₁₀ aryl optionally substituted with one or 5 more substituents selected from oxo, -OR², SR², -R², -N(R²)₂, -R²-OH, -CN, -CO₂R², -C(O)-N(R²)₂, -S(O)₂-N(R²)₂, -N(R²)-C(O)-R², -C(O)-R², -S(O)_n-R², -OCF₃, -S(O)_n-Q, methylenedioxy, -N(R²)-S(O)₂(R²), halo, -CF₃, -NO₂, Q, -OQ, -OR⁷, -SR⁷, -R⁷, -N(R²)(R⁷) or -N(R⁷)₂; or a 5-membered 10 heterocyclic ring containing one S and optionally containing N as an additional heteroatom, wherein said heterocyclic ring is optionally substituted with one to two groups independently selected from -CH₃, R⁴, or Ht.

Ht, insofar as it is defined as part of R³, is 15 defined as above except for the exclusion of heterocycles; and

all other variables are as defined for formula I.

Even more preferred are compounds of formula XXII, wherein A is 3-tetrahydrofuryl-O-C(O)-; G is 20 hydrogen; D' is isobutyl; E is phenyl substituted with N(R⁷)₂; each M is independently selected from H, Li, Na, K, Mg, Ca, Ba, C₁-C₄ alkyl or -N(R²)₄; and each M' is H or C₁-C₄ alkyl.

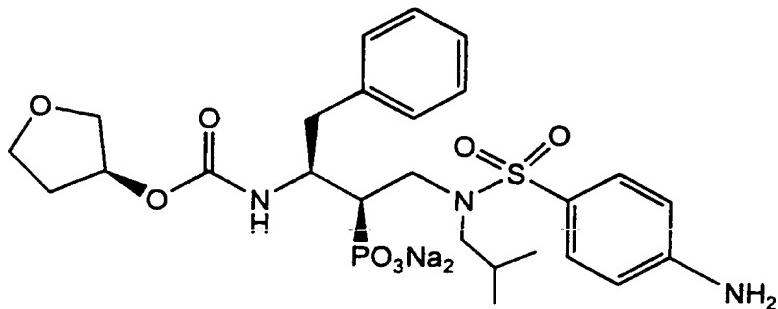
Another preferred embodiment for the formula 25 XXII compounds are those wherein:

E is a 5-membered heterocyclic ring containing one S and optionally containing N as an additional heteroatom, wherein said heterocyclic ring is optionally substituted with one to two groups independently selected from -CH₃, 30 R⁴, or Ht; and

all other variables are as defined for formula I.

Even more preferred are any of the formula XXII compounds set forth above, wherein R⁷ in -OR⁷ is -PO(OM)₂, or C(O)CH₂OCH₂CH₂OCH₂CH₂OCH₃ and both R⁷ in -N(R⁷)₂ are H, wherein M is H, Li, Na, K or C₁-C₄ alkyl; or wherein R⁷ in -OR⁷ is C(O)CH₂OCH₂CH₂OCH₃, one R⁷ in -N(R⁷)₂ is C(O)CH₂OCH₂CH₂OCH₃ and the other is H.

The most preferred compound of formula XXII has the structure:



For compounds of formula XXIII, most preferred compounds are those wherein:

R³ is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₅-C₆ cycloalkyl, C₅-C₆ cycloalkenyl or a 5-6 membered saturated or unsaturated heterocycle, wherein any member of said R³ may be optionally substituted with one or more substituents selected from the group consisting of -OR², -C(O)-NH-R², -S(O)_nN(R²)(R²), Ht, -CN, -SR², -C(O)₂R² and NR²-C(O)-R²; and D' is C₁-C₃ alkyl or C₃ alkenyl, wherein said alkyl or alkenyl may optionally be substituted with one or more groups selected from the group consisting of C₃-C₆ cycloalkyl, -OR², -O-Q and Q (with all other variables being defined as above for compounds of formula I).

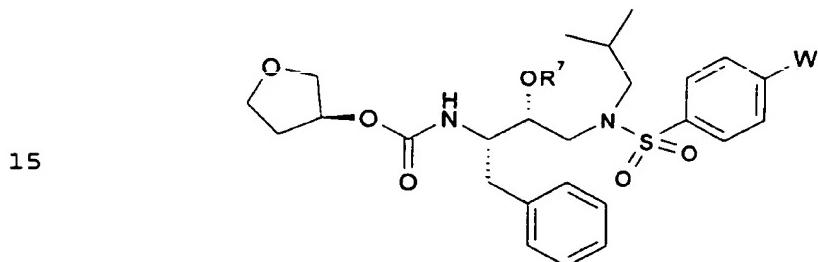
Even more preferred are compounds of formula XXIII described above, wherein R⁷ is -PO(OM)₂ or -C(O)-M'.

For compounds of formula XXXI, most preferred compounds are those wherein A is R¹-Ht, each R³ is

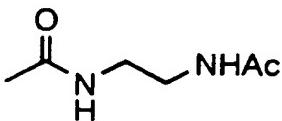
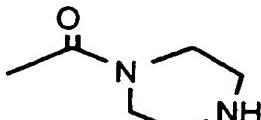
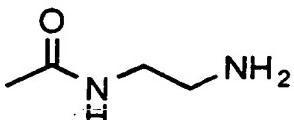
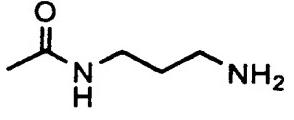
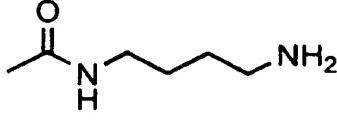
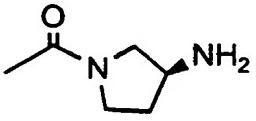
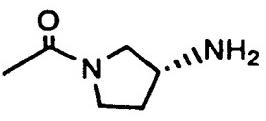
independently C₁-C₆ alkyl which may be optionally substituted with a substituent selected from the group consisting of -OR², -C(O)-NH-R², -S(O)_nN(R²)(R²), Ht, -CN, -SR², -CO₂R² or -NR²-C(O)-R²; and D' is C₁-C₄ alkyl, which 5 may be optionally substituted with a group selected from the group consisting of C₃-C₆ cycloalkyl, -OR², -O-Q; and E is Ht, Ht-Ht and -NR²R³.

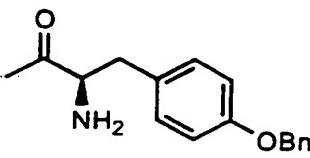
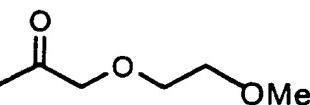
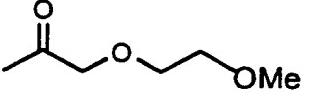
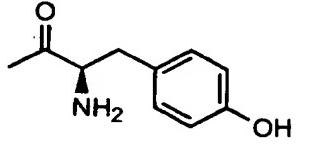
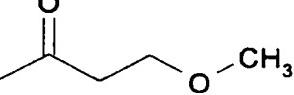
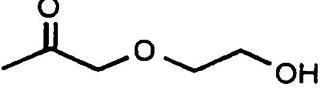
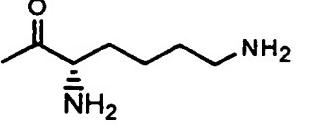
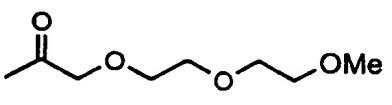
Even more preferred are those compounds of formula XXXI described above wherein R⁷ is -PO(OM)₂ or 10 -C(O)-M'.

TABLE I

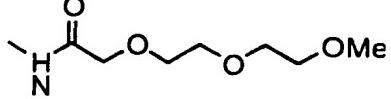
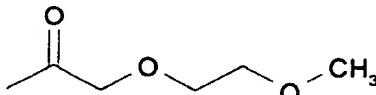
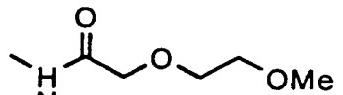
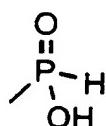
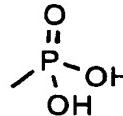
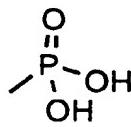
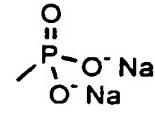
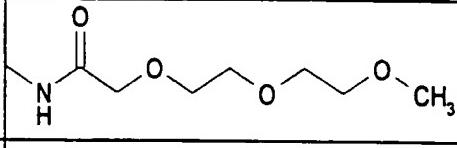
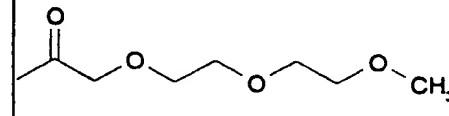
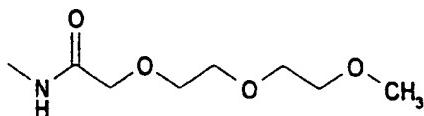


CMPD	R ⁷	W
198		-NO ₂
199		-NH ₂
200		-NH ₂

CMPD	R ⁷	W
201		-NH ₂
202		-NH ₂
203		-NH ₂
204		-NH ₂
205		-NH ₂
206		-NH ₂
207		-NH ₂

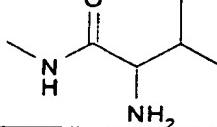
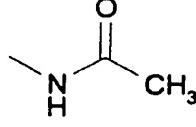
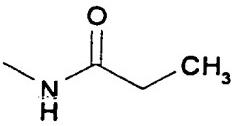
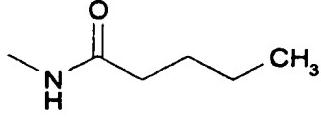
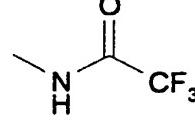
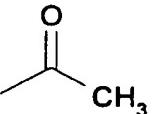
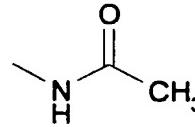
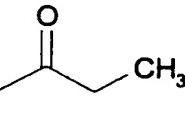
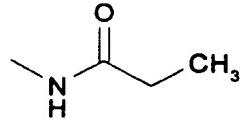
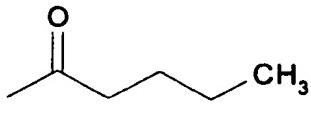
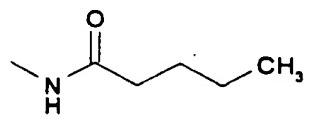
CMPD	R ⁷	W
208		-NO ₂
209		-NO ₂
210		-NH ₂
211		-NH ₂
212		-NH ₂
213		-NH ₂
214		-NH ₂
215		-NH ₂

CMPD	R ⁷	W
216		-NH ₂
217		-NH ₂
219	H	
220	H	
221	H	
222	H	
223	H	

CMPD	R ⁷	W
224	H	
225		
226		-NO ₂
227		-NO ₂
228		-NH ₂
229		-NH ₂
230	H	
231		

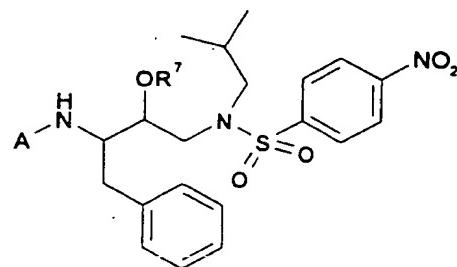
CMPD	R ⁷	W
237		-NO ₂
238		-NO ₂
239	-SO ₃ H	-NO ₂
240	-SO ₃ H	-NH ₂
241		-NO ₂
242		-NH ₂
245		-NH ₂

CMPD	R ⁷	W
246		-NH ₂
247		-NH ₂
248		-NH ₂
249		-NH ₂
250		-NH ₂
251		-NH ₂
252		-NH ₂
253		-NH ₂
254		-NH ₂

CMPD	R ⁷	W
255	H	-NH-CHO
256	H	
257	H	
258	H	
259	H	
260	H	
261		
262		
263		
264	PO ₃ K ₂	-NH ₂

CMPD	R ⁷	W
265	PO ₃ Ca	-NH ₂
266	PO ₃ Mg	-NH ₂
267		-NH ₂
308		-NH ₂
402	H	
403	H	
404	H	
405	H	
406	H	
407	H	

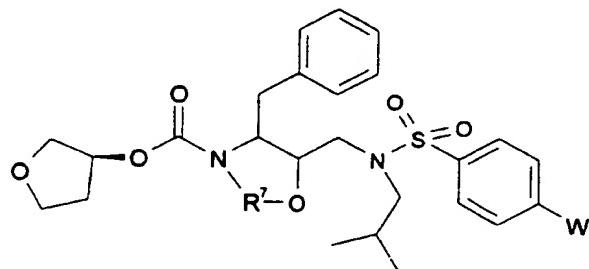
CMPD	R ⁷	W
408	$\text{H}_3\text{C}-\overset{\underset{\text{O}}{\parallel}}{\text{P}}-\text{OH}$	-NH ₂

TABLE II

5

COMPOUND	A	R ⁷
232	$\begin{array}{c} \text{H}_3\text{C} \\ \\ \text{H}_3\text{C}-\text{C}-\text{O} \\ \\ \text{CH}_3 \end{array}$	$\begin{array}{c} \text{O} \\ \\ \text{C}-\text{O}-\text{CH}_3 \end{array}$
233	H	$\begin{array}{c} \text{O} \\ \\ \text{C}-\text{O}-\text{CH}_3 \end{array}$
234	$\begin{array}{c} \text{H}_3\text{C} \\ \\ \text{H}_3\text{C}-\text{C}-\text{O} \\ \\ \text{C} \end{array}$	H
235	$\begin{array}{c} \text{H}_3\text{C} \\ \\ \text{H}_3\text{C}-\text{C}-\text{O} \\ \\ \text{CH}_3 \end{array}$	$\begin{array}{c} \text{O} \\ \\ \text{C}-\text{O}-\text{C}_6\text{H}_3\text{NO}_2 \end{array}$

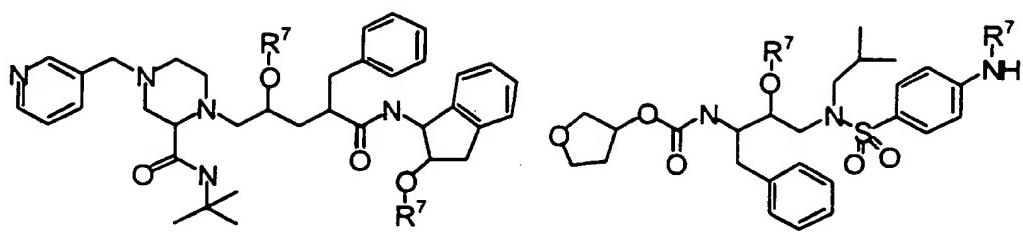
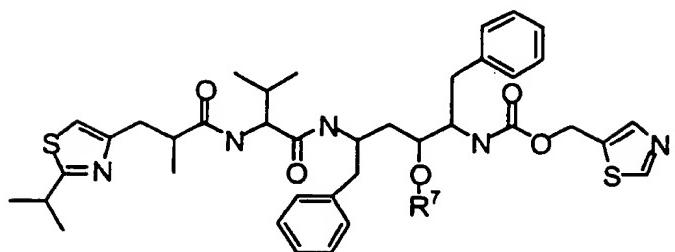
COMPOUND	A	R ⁷
236	<p>Chemical structure A: 2-methylpropyl acetate. It consists of a central carbon atom bonded to a methyl group (CH₃) at the top, another methyl group (CH₃) to its right, an ethyl group (-CH₂CH₃) below it, and an acetoxy group (-OAc) to its left.</p>	<p>Chemical structure R⁷: 2-acetyl-1,3-dioxolan-2-ylmethyl group. It features a four-membered dioxolan ring with a carbonyl group (C=O) at position 1 and a methylene group (-CH₂-) at position 2. Attached to the ring is a carbonyl group (C=O) which is further substituted with a methyl group (CH₃).</p>

TABLE III

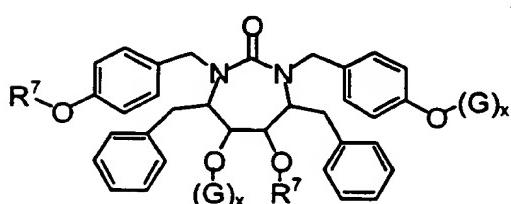
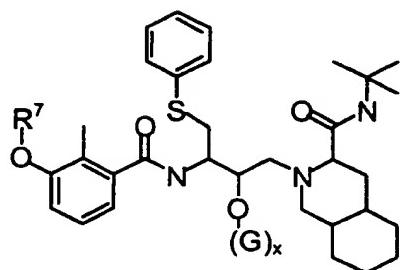
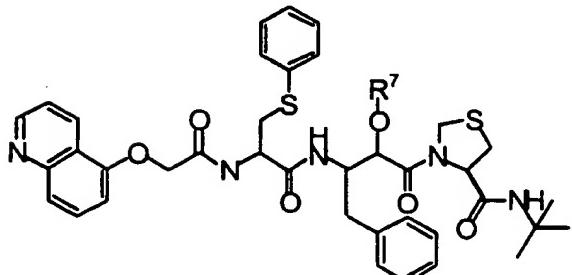
5

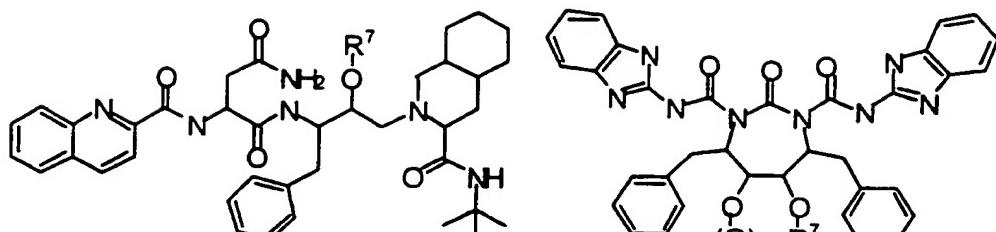
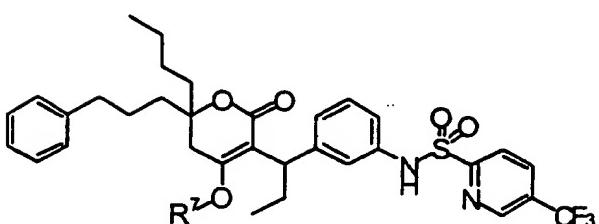
COMPOUND	R ⁷	W
243	<p>Chemical structure R⁷ for compound 243: methylphosphoryl group. It consists of a phosphorus atom (P) bonded to three hydrogen atoms (H) and one methyl group (-CH₃). The phosphorus atom is also bonded to an oxygen atom (O) with a double bond.</p>	-NO ₂
244	<p>Chemical structure R⁷ for compound 244: methylaminophosphoryl group. It consists of a phosphorus atom (P) bonded to three hydrogen atoms (H) and one methyl group (-CH₃). The phosphorus atom is also bonded to an amino group (-NH₂) and an oxygen atom (O) with a double bond.</p>	-NH ₂
400	<p>Chemical structure R⁷ for compound 400: hydroxymethylphosphoryl group. It consists of a phosphorus atom (P) bonded to three hydrogen atoms (H) and one methyl group (-CH₃). The phosphorus atom is also bonded to a hydroxyl group (-OH) and an oxygen atom (O) with a double bond.</p>	-NO ₂
401	<p>Chemical structure R⁷ for compound 401: aminohydroxymethylphosphoryl group. It consists of a phosphorus atom (P) bonded to three hydrogen atoms (H) and one methyl group (-CH₃). The phosphorus atom is also bonded to a hydroxyl group (-OH), an amino group (-NH₂), and an oxygen atom (O) with a double bond.</p>	-NH ₂

According to another embodiment, the invention provides compounds of the following formulae:

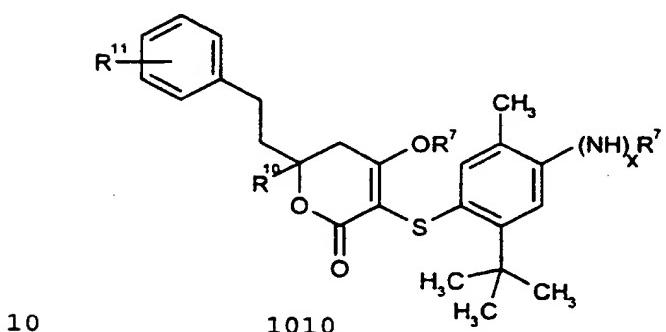
10011002

5

1003100410051006

10071008

5

1009 , or

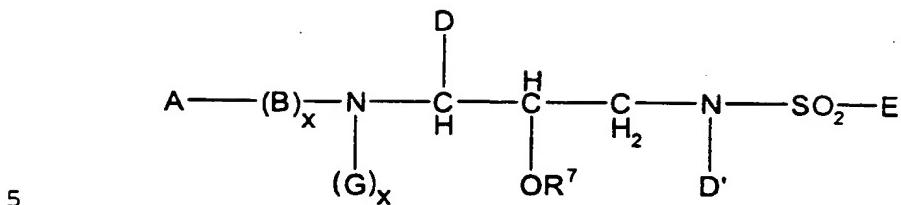
10

1010

wherein, in compound 1005, when R⁷ is PO₃M, (G)_x is not H; and wherein R¹⁰ is selected from isopropoyl or cyclopentyl; R¹¹ is selected from NHR⁷ or OR⁷; and x, R⁷ and G are as defined above.

15

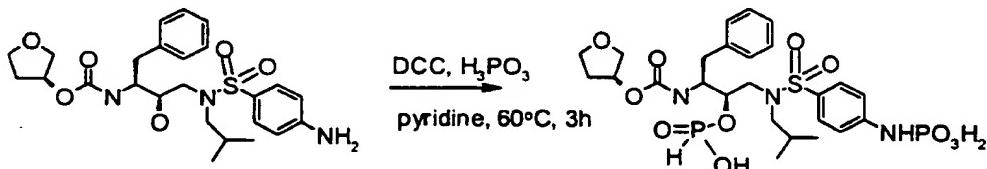
The prodrugs of the present invention may be synthesized using conventional synthetic techniques. United States patent 5,585,397 discloses the synthesis of compounds of formula:



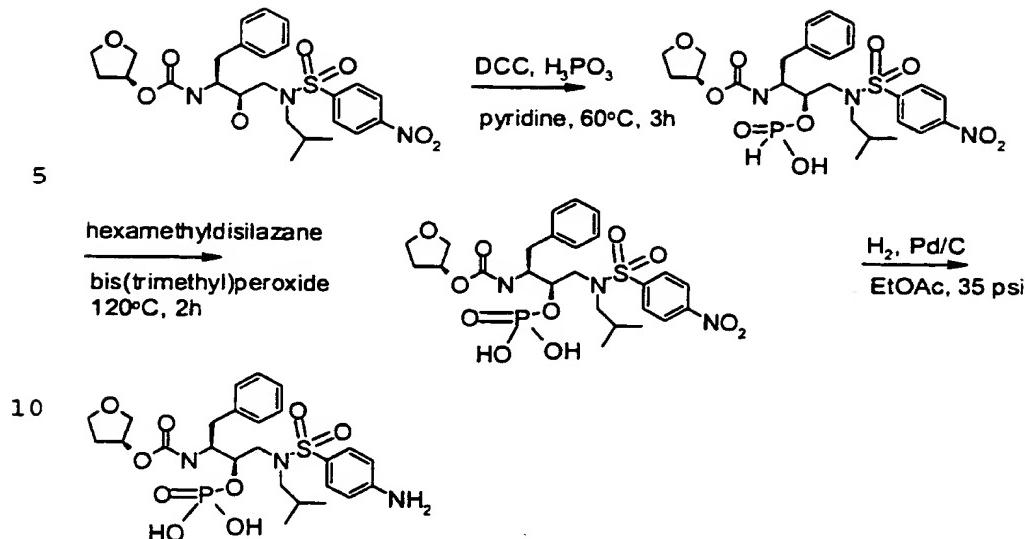
wherein A, B, n, D, D', and E are as defined above.

Prodrugs of formula (I) of the present invention can be readily synthesized from the '397 compounds using conventional techniques. One of skill in the art would 10 be well aware of conventional synthetic reagents to convert the -OH group of the '397 compounds to a desired -OR⁷ functionality of the present invention, wherein R⁷ is as defined above. The relative ease with which the compounds of this invention can be synthesized represents 15 an enormous advantage in the large scale production of these compounds.

For example, VX-478, a compound disclosed in the '397 patent, can be readily converted to the corresponding bis-phosphate ester derivative, as shown below:

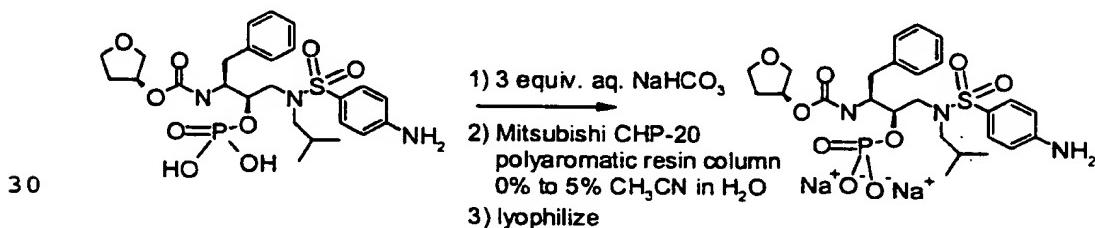


25 Alternatively, if the monophosphate ester of
VX-478 is desired, then the synthetic scheme can be
readily adapted by beginning with the 4-nitrophenyl
derivative of VX-478, as shown below:



Examples of specific compounds in addition to
 15 VX-478 which may be converted to the prodrugs of this
 invention by similar techniques (and the syntheses of
 those intermediates to the compounds of the present
 invention) are disclosed in WO 94/05639 and WO 96/33184,
 the disclosures of which are herein incorporated by
 20 reference.

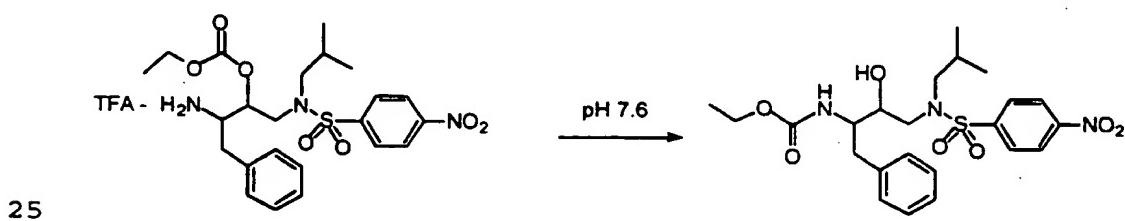
Pharmaceutically acceptable salts of the
 compounds of the present invention may be readily
 prepared using known techniques. For example, the
 disodium salt of the mono-phosphate ester shown above can
 25 be prepared as shown below:



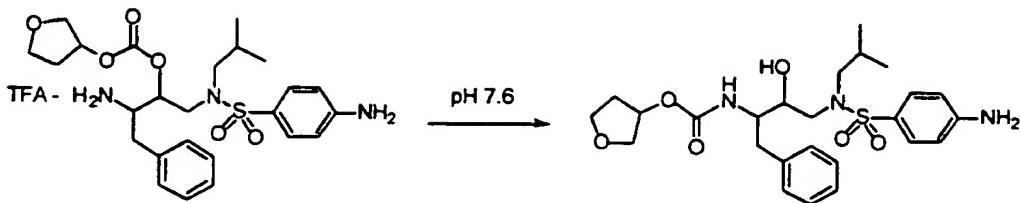
The compounds of this invention may be modified by appending appropriate functionalities to enhance selective biological properties. Such modifications are known in the art and include those which increase 5 biological penetration into a given biological system (e.g., blood, lymphatic system, central nervous system), increase oral availability, increase solubility to allow administration by injection, alter metabolism and alter rate of excretion.

Without being bound by theory, we believe that 10 two different mechanisms are involved in converting the prodrugs of this invention into the active drug, depending upon the structure of the prodrug. The first mechanism involves the enzymatic or chemical 15 transformation of the prodrug species into the active form. The second mechanism involves the enzymatic or chemical cleavage of a functionality on the prodrug to produce the active compound.

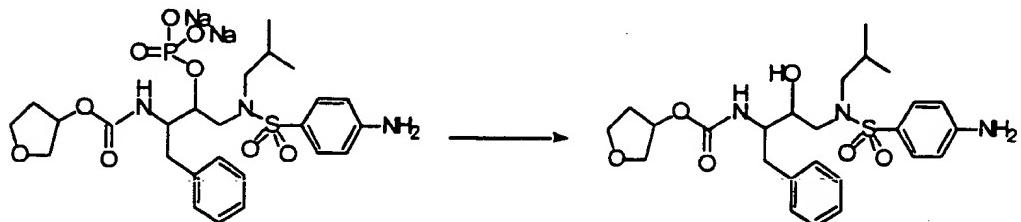
The chemical or enzymatic transformation can 20 involve transfer of a functional group (i.e., R⁷) from one heteroatom within the molecule to another heteroatom. This transfer is demonstrated in the chemical reactions shown below:



and



The cleavage mechanism is demonstrated by the reaction below where a phosphate ester-containing prodrug is converted into the active form of the drug by removal 5 of the phosphate group.



These protease inhibitors and their utility as inhibitors of aspartyl proteases are described in United States Patent 5,585,397, the disclosure of which is incorporated herein by reference.

10 The prodrugs of the present invention are characterized by unexpectedly high aqueous solubility. This solubility facilitates administration of higher doses of the prodrug, resulting in a greater drug load per unit dosage. The prodrugs of the present invention 15 are also characterized by facile hydrolytic cleavage to release the active aspartyl protease inhibitor in vivo. The high aqueous solubility and the facile in vivo metabolism result in a greater bioavailability of the drug. As a result, the pill burden on a patient is 20 significantly reduced.

The prodrugs of this invention may be employed in a conventional manner for the treatment of viruses, such as HIV and HTLV, which depend on aspartyl proteases

for obligatory events in their life cycle. Such methods of treatment, their dosage levels and requirements may be selected by those of ordinary skill in the art from available methods and techniques. For example, a prodrug 5 of this invention may be combined with a pharmaceutically acceptable adjuvant for administration to a virally-infected patient in a pharmaceutically acceptable manner and in an amount effective to lessen the severity of the viral infection.

10 Alternatively, the prodrugs of this invention may be used in vaccines and methods for protecting individuals against viral infection over an extended period of time. The prodrugs may be employed in such vaccines either alone or together with other compounds of 15 this invention in a manner consistent with the conventional utilization of protease inhibitors in vaccines. For example, a prodrug of this invention may be combined with pharmaceutically acceptable adjuvants conventionally employed in vaccines and administered in 20 prophylactically effective amounts to protect individuals over an extended period time against HIV infection. As such, the novel protease inhibitors of this invention can be administered as agents for treating or preventing HIV infection in a mammal.

25 The prodrugs of this invention may be administered to a healthy or HIV-infected patient either as a single agent or in combination with other anti-viral agents which interfere with the replication cycle of HIV. By administering the compounds of this invention with 30 other anti-viral agents which target different events in the viral life cycle, the therapeutic effect of these compounds is potentiated. For instance, the co-

administered anti-viral agent can be one which targets early events in the life cycle of the virus, such as cell entry, reverse transcription and viral DNA integration into cellular DNA. Anti-HIV agents targeting such early 5 life cycle events include, didanosine (ddI), alcitabine (ddC), d4T, zidovudine (AZT), polysulfated polysaccharides, sT4 (soluble CD4), ganclovir, dideoxycytidine, trisodium phosphonoformate, eflornithine, ribavirin, acyclovir, alpha interferon and tri- 10 menotrexate. Additionally, non-nucleoside inhibitors of reverse transcriptase, such as TIBO or nevirapine, may be used to potentiate the effect of the compounds of this invention, as may viral uncoating inhibitors, inhibitors of trans-activating proteins such as tat or rev, or 15 inhibitors of the viral integrase.

Combination therapies according to this invention exert a synergistic effect in inhibiting HIV replication because each component agent of the combination acts on a different site of HIV replication. 20 The use of such combinations also advantageously reduces the dosage of a given conventional anti-retroviral agent which would be required for a desired therapeutic or prophylactic effect as compared to when that agent is administered as a monotherapy. These combinations may 25 reduce or eliminate the side effects of conventional single anti-retroviral agent therapies while not interfering with the anti-retroviral activity of those agents. These combinations reduce potential of resistance to single agent therapies, while minimizing 30 any associated toxicity. These combinations may also increase the efficacy of the conventional agent without increasing the associated toxicity. In particular, we

have discovered that these prodrugs act synergistically in preventing the replication of HIV in human T cells. Preferred combination therapies include the administration of a prodrug of this invention with AZT,
5 ddI, ddC or d4T.

Alternatively, the prodrugs of this invention may also be co-administered with other HIV protease inhibitors such as Ro 31-8959 (Roche), L-735,524 (Merck), XM 323 (Du-Pont Merck) and A-80,987 (Abbott) to increase
10 the effect of therapy or prophylaxis against various viral mutants or members of other HIV quasi species.

We prefer administering the prodrugs of this invention as single agents or in combination with retroviral reverse transcriptase inhibitors, such as
15 derivatives of AZT, or other HIV aspartyl protease inhibitors. We believe that the co-administration of the compounds of this invention with retroviral reverse transcriptase inhibitors or HIV aspartyl protease inhibitors may exert a substantial synergistic effect,
20 thereby preventing, substantially reducing, or completely eliminating viral infectivity and its associated symptoms.

The prodrugs of this invention can also be administered in combination with immunomodulators (e.g.,
25 bropirimine, anti-human alpha interferon antibody, IL-2, GM-CSF, methionine enkephalin, interferon alpha, diethyldithiocarbamate, tumor necrosis factor, naltrexone and rEPO); and antibiotics (e.g., pentamidine isethiorate) to prevent or combat infection and disease
30 associated with HIV infections, such as AIDS and ARC.

When the prodrugs of this invention are administered in combination therapies with other agents,

they may be administered sequentially or concurrently to the patient. Alternatively, pharmaceutical or prophylactic compositions according to this invention may be comprised of a combination of a prodrug of this 5 invention and another therapeutic or prophylactic agent.

Although this invention focuses on the use of the prodrugs disclosed herein for preventing and treating HIV infection, the compounds of this invention can also be used as inhibitory agents for other viruses which 10 depend on similar aspartyl proteases for obligatory events in their life cycle. These viruses include, as well as other AIDS-like diseases caused by retroviruses, such as simian immunodeficiency viruses, but are not limited to, HTLV-I and HTLV-II. In addition, the 15 compounds of this invention may also be used to inhibit other aspartyl proteases, and in particular, other human aspartyl proteases, including renin and aspartyl proteases that process endothelin precursors.

Pharmaceutical compositions of this invention 20 comprise any of the compounds of the present invention, and pharmaceutically acceptable salts thereof, with any pharmaceutically acceptable carrier, adjuvant or vehicle. Pharmaceutically acceptable carriers, adjuvants and vehicles that may be used in the pharmaceutical 25 compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of 30 saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium

chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes,
5 polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

The pharmaceutical compositions of this invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, 10 vaginally or via an implanted reservoir. We prefer oral administration or administration by injection. The pharmaceutical compositions of this invention may contain any conventional non-toxic pharmaceutically-acceptable carriers, adjuvants or vehicles. The term parenteral as 15 used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intra-articular, intrasynovial, intrasternal, intrathecal, intralesional and intracranial injection or infusion techniques.

The pharmaceutical compositions may be in the 20 form of a sterile injectable preparation, for example, as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as, for example, Tween 80) and suspending 25 agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are mannitol, 30 water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For

this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural 5 pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant such as Ph. Helv or a similar alcohol.

10 The pharmaceutical compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, and aqueous suspensions and solutions. In the case of tablets for oral use, carriers which are

15 commonly used include lactose and corn starch.

Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions are administered 20 orally, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring and/or coloring agents may be added.

The pharmaceutical compositions of this 25 invention may also be administered in the form of suppositories for rectal administration. These compositions can be prepared by mixing a compound of this invention with a suitable non-irritating excipient which is solid at room temperature but liquid at the rectal 30 temperature and therefore will melt in the rectum to release the active components. Such materials include,

but are not limited to, cocoa butter, beeswax and polyethylene glycols.

Topical administration of the pharmaceutical compositions of this invention is especially useful when 5 the desired treatment involves areas or organs readily accessible by topical application. For application topically to the skin, the pharmaceutical composition should be formulated with a suitable ointment containing the active components suspended or dissolved in a 10 carrier. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petroleum, white petroleum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water. Alternatively, the 15 pharmaceutical composition can be formulated with a suitable lotion or cream containing the active compound suspended or dissolved in a carrier. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl 20 alcohol, 2-octyldodecanol, benzyl alcohol and water. The pharmaceutical compositions of this invention may also be topically applied to the lower intestinal tract by rectal suppository formulation or in a suitable enema formulation. Topically-transdermal patches are also 25 included in this invention.

The pharmaceutical compositions of this invention may be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical 30 formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability,

fluorocarbons, and/or other solubilizing or dispersing agents known in the art.

Dosage levels of between about .01 and about 100 mg/kg body weight per day, preferably between about 5 0.5 and about 50 mg/kg body weight per day of the active ingredient compound are useful in the prevention and treatment of viral infection, including HIV infection. Typically, the pharmaceutical compositions of this invention will be administered from about 1 to about 10 5 times per day or alternatively, as a continuous infusion. Such administration can be used as a chronic or acute therapy. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and 15 the particular mode of administration. A typical preparation will contain from about 5% to about 95% active compound (w/w). Preferably, such preparations contain from about 20% to about 80% active compound.

Upon improvement of a patient's condition, a 20 maintenance dose of a compound, composition or combination of this invention may be administered, if necessary. Subsequently, the dosage or frequency of administration, or both, may be reduced, as a function of the symptoms, to a level at which the improved condition 25 is retained when the symptoms have been alleviated to the desired level, treatment should cease. Patients may, however, require intermittent treatment on a long-term basis upon any recurrence of disease symptoms.

As the skilled artisan will appreciate, lower 30 or higher doses than those recited above may be required. Specific dosage and treatment regimens for any particular patient will depend upon a variety of factors, including

the activity of the specific compound employed, the age, body weight, general health status, sex, diet, time of administration, rate of excretion, drug combination, the severity and course of the infection, the patient's 5 disposition to the infection and the judgment of the treating physician.

In order that this invention be more fully understood, the following examples are set forth. These examples are for the purpose of illustration only and are 10 not to be construed as limiting the scope of the invention in any way.

Example 1

General conditions:

(A) Analytical HPLC 0-100% B/30 min, 1.5 mL/min,
15 A=0.1% TFA in water, B=0.1% TFA in acetonitrile.

Detection at 254 and 220 nm, C18 reverse phase Vydac,
 $t_0=2.4$ min.

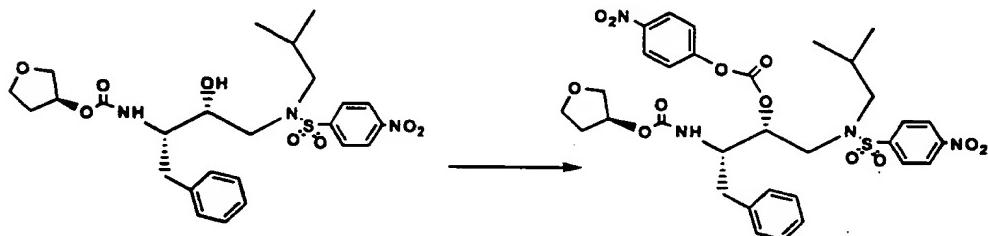
(B) 1/3 v/v EtOAc/hexane

(C) 1/2 v/v EtOAc/hexane

20 (D) Analytical HPLC 0-100% B/10 min, 1.5 mL/min,
A=0.1% TFA in water, B=0.1% TFA in acetonitrile.

Detection at 254 and 220 nm, C18 reverse phase Vydac,
 $t_0=2.4$ min.

25



A mixture of 2.0g (3.7 mMol) of 197 and 3.0g

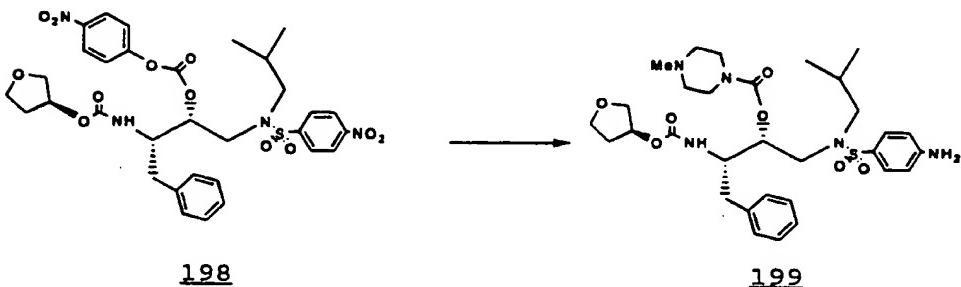
(16 mMol) of di-p-nitrophenyl carbonate in 10 ml of dimethylformamide was treated at 25° with 4 ml (4 mMol) of P4-phosphazene base (Fluka, 1M in hexane). The mixture was stirred for 6h at 25° until all of the starting alcohol was consumed. The reaction mixture was partitioned between ethyl acetate and 1N hydrochloric acid. The organic layer was washed with 1N sodium hydroxide and brine, dried over magnesium sulfate and concentrated in vacuo. Titration with dichloromethane gave the desired mixed carbonate (1.2g crop1 and 0.6g crop 2) as a fine powder. Combined yield: 69%. Rf=0.13 (1/3 EtOAc/hexane, conditions B), Rf=0.40 (1/2 EtOAc/hexane, conditions C), tHPLC=23.83 min (A), MS (ES+) 701 (M+1).

1H-NMR (CDCl₃): 0.82 (6H, dd), 1.9 (2H, m), 2.15 (1H, m), 2.8 (1H, m), 3.0 (4H, m), 3.5 (2H, m), 3.6 (1H, m), 3.8 (4H, m), 4.3 (1H, bs), 4.8 (1H, m), 5.17 (2H, m), 7.7 (7H, m), 7.95 (2H, d), 8.35 (4H, m).

13C (CDCl₃): 155.2, 152.2, 149.9, 145.6, 135.9, +129.0, +128.8, +128.5, +127.2, +125.4, +124.4, +121.8, +78.1, +75.8, -73.1, -66.9, -56.5, +52.7, -48.2, -35.9, -35.9, 32.6, -+26.4, +19.9, +19.8.

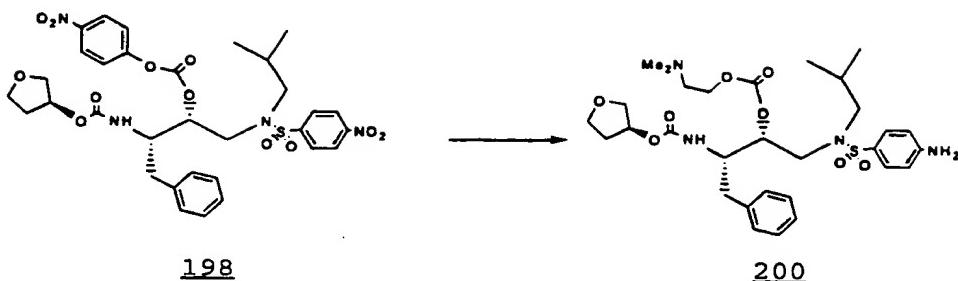
Example 2

25



To 0.20g (0.286 mM) of 198 dissolved in 3 ml of THF was added 0.11 g (1.14 mM) of 1-Methyl-piperidine and the mixture was stirred overnight at room temperature ("rt"). All the solvents were then evaporated and the 5 solid residue partitioned between EtOAc and water. The volatiles were removed and, where appropriate, the residue was treated with 1:1 TFA/DCM over 30 min at rt to remove the Boc protecting group. The product was dissolved in 0.25 ml TFA and 1.5 ml THF. Hydrogenolysis 10 for 10 hours in presence of 30 mg of 10% Pd/C gave the desired compound. The final purification was on preparative reversed phase C18 using conditions Example 1, except that the flow rate was 18 ml/min.

C,H,N: calc: 49.27, 5.57, 8.25, found 49.15, 5.76, 8.29
15 C₃₁H₄₅N₅O₇S₁ . 1.9CF₃COOH
LC/MS (ES+) 632 (M+1) 1 peak at 4.71 min
Analytical HPLC(A) t=N/A min
1H: 0.71 (3H,d), 0.74 (3H,d), 1.80 (2H,m), 2.03 (1H,m),
2.63 (2H,m), 2.74 (1H,m), 2.82 (3H,s), 2.92 (2H,m), 3.20
20 (4H,m), 3.42 (3H,m), 3.62 (2H,m), 3.75 (1H,m), 4.05
(3H,m), 4.97 (2H,m), 6.2 (1H,bs), 6.60 (2H,m), 7.22
(5H,m), 7.40 (3H,m),
13C (DMSO): 156.4, 154.0, 153.8, 138.8, 129.6, 129.5,
128.3, 126.5, 123.7, 112.7, 74.8, 72.9, 66.7, 58.2, 54.0,
25 53.1, 49.3, 42.3, 40.8, 36.0, 33.3, 25.8, 20.4, 20.3

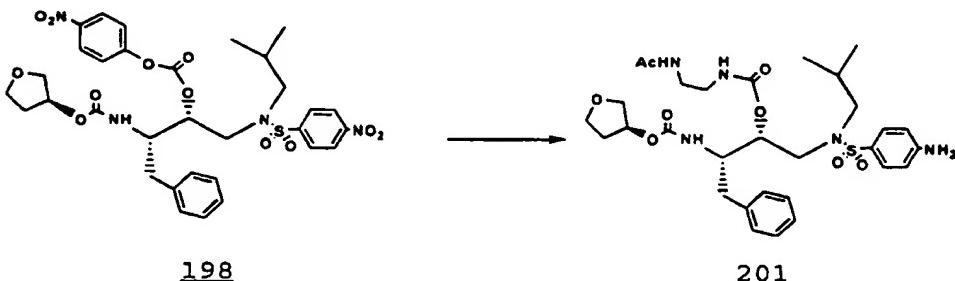
Example 3

The synthesis of compound 200 from compound 198

5 was carried as described in Example 1, except that N,N-dimethyl-aminoethanol was used in place of di-p-nitrophenyl carbonate.

1H NMR (acetone-d6): 0.82 (6H, dd), 1.83 (2H, m), 2.07 (1H, m), 2.64 (2H, m), 2.82 (6H, s), 2.90 (2H, m), 3.19 (1H, m), 3.38 (4H, m), 3.63 (2H, m), 3.76 (1H, m), 4.17 (2YH, m), 4.40 (1H, m), 4.56 (1H, m), 4.96 (1H, m), 5.06 (1H, m), 6.06 (1H, d), 6.68 (2H, d), 7.23 (5H, m), 7.47 (2H, d).
 13C NMR (acetone d6): 20.2, 20.3, 27.5, 33.4, 35.6, 43.8, 50.1, 54.2, 56.4, 58.5, 63.1, 67.4, 73.6, 76.2, 79.9, 114.2, 118.3, 127.4, 129.2, 130.1, 130.3, 139.3, 153.4, 157.0.
 LC/MS: 1 peak, 621 (MH+).

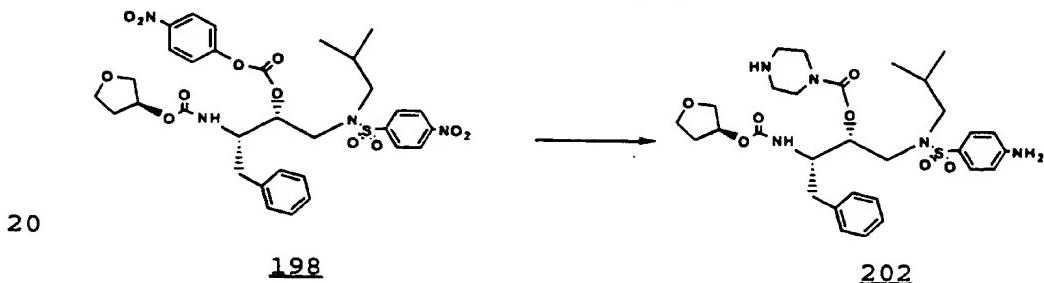
20

Example 4

The synthesis of compound 201 from compound 198 was carried as described in Example 1, except that N-acetyl-ethylenediamine was used in place of di-p-nitrophenyl carbonate.

- 5 C,H,N: calc: 49.66, 5.64, 8.83, found 49.76, 5.98, 8.93
 $\text{C}_{30}\text{H}_{43}\text{N}_5\text{O}_8\text{S}_1$. 1.4CF₃COOH.
 LC/MS (ES+) 634 (M+1) 1 peak at 5.08 min.
 Analytical HPLC(A) t=15.92 min.
 10 1H: d-3 acetonitrile: 0.88 (6H,dd), 1.92 (3H,s), 1.94
 (2H,m), 2.17 (1H,m), 2.72 (2H,m), 2.96 (2H,m), 3.07
 (3H,m), 3.29 (1H,m), 3.42 (3H,m), 3.69 (1H,m), 3.77
 (1H,m), 3.82 (1H,m), 4.133 (1H,m), 4.40 (1H,bs), 5.05
 (2H,m), 5.80 (1H,m), 6.10 (1H,d), 6.78 (2H,d), 6.83
 (1H,bs), 7.28 (5H,m), 7.58 (2H,d).
 13C (d3-acetonitrile): 157.1, 157.0, 153.2, 139.6, +130.3,
 +130.2, +129.2, +127.2, 126.2, +114.2, +76.0, +75.4, -
 73.6, -67.4, -58.2, +54.9, -50.2, -41.6, -39.8, -35.9, -
 33.4, +27.3, +23.1, +20.4, +20.2.

Example 5



20

198

202

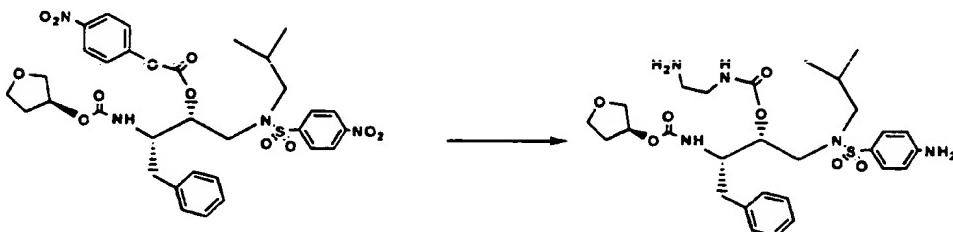
The synthesis of compound 202 from compound 198
was carried as described in Example 1, except that mono
N-Boc-piperazine was used in place of di-*p*-nitrophenyl
carbonate.

C,H,N: calc: 48.28, 5.68, 8.41, found 48.28, 5.36, 8.28
 $\text{C}_{30}\text{H}_{43}\text{N}_5\text{O}_7\text{S}_1 \times 2 \text{ CF}_3\text{COOH}$
 LC/MS (ES+) 618 (M+1) 1 peak at 4.36 min.

Analytical HPLC(A) t=14.84 min.

1H: d6-DMSO: 0.72 (3H,d), 0.77 (3H,d), 1.78 (2H,m), 2.09
 (1H,m), 2.64 (2H,m), 2.73 (1H,m), 2.80 (1H,m), 3.08
 (4H,m), 3.32 (2H,m), 3.41 (1H,m), 3.50 (4H,m), 3.54
 5 (1H,m), 3.63 (1H,m), 3.70 (1H,m), 3.98 (1H,m), 4.89
 (1H,m), 4.97 (1H,m), 6.61 (2H,d), 7.23 (5H,m), 7.42
 (3H,m), 8.88 (2H,bs).
 13C: (DMSO): 155.7, 153.6, 153.0, 138.4, +129.1, +129.0,
 +128.1, +126.1, 123.2, +112.7, +75.2, +74.4, -72.5,
 10 -66.2, -56.9, +53.1, -48.8, -42.5, -40.8, -35.0, -32.2,
 +26.2, +20.0, +19.8.

Example 6



198

203

15 The synthesis of compound 203 from compound 198 was carried as described in Example 1, except that mono-N-Boc-ethylenediamine was used in place of di-p-nitrophenyl carbonate.

C,H,N: calc: 46.89, 5.29, 8.54, found 46.50, 5.51, 8.54
 20 C₂₈H₄₁N₅O₂S₁ x 2 CF₃COOH.

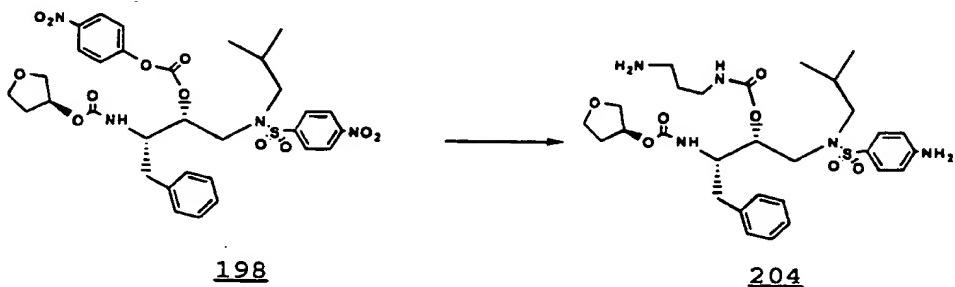
LC/MS (ES+) 592 (M+1) 1 peak at 4.32 min.

Analytical HPLC(A) t=14.69 min.

1H:d-6 DMSO: 0.77 (6H,d), 1.82 (2H,m), 2.06 (1H,m), 2.57
 (2H,m), 2.82 (4H,m), 2.97 (1H,m), 3.30 (5H,m), 3.55
 25 (1H,m), 3.65 (1H,m), 3.70 (1H,m), 3.95 (1H,m), 4.88
 (1H,m), 4.95 (1H,m), 6.62 (2H,d), 7.20 (6H,m), 7.39
 (3H,m), 7.78 (3H,bs).

¹³C (dmso): 155.9, 152.9, 138.5, 129.2, 128.9, 128.1, 126.1, 122.9, 112.7, 74.7, 74.5, 72.6, 66.2, 57.2, 53.2, 49.4, 38.8, 37.94, 35.1, 32.1, 26.3, 20.0, 19.8.

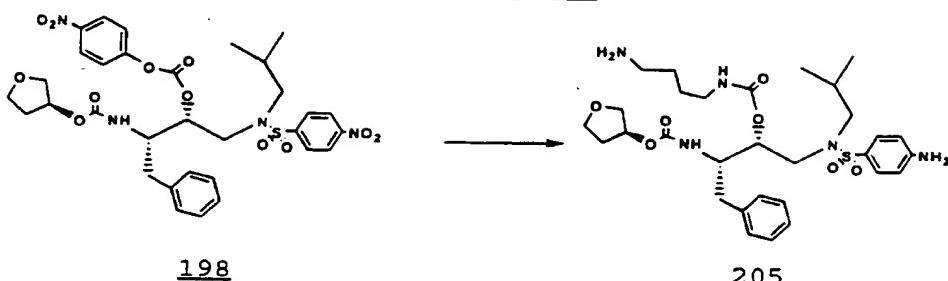
5

Example 7

The synthesis of compound 204 from compound 198 was carried as described in Example 1, except that mono-
10 1,3-diamino-3-N-Boc-propane was used in place of di-p-nitrophenyl carbonate.

C,H,N: calc: 49.07, 5.64, 8.89, found 48.95, 6.00, 8.92
C₂₉H₄₃N₅O₇S₁ × 1.6 CF₃COOH
LC/MS (ES+) 605 (M+1) 1 peak at 4.27 min.

15 Analytical HPLC(A) t=14.72 min.
1H:d-6 DMSO: 0.78 (6H,dd), 1.64 (2H,m), 1.83 (2H,m), 2.03 (1H,m), 2.57 (1H,m), 2.78 (4H,m), 2.94 (1H,m), 3.03 (2H,m), 3.32 (2H,m), 3.58 (1H,m), 3.63 (1H,m), 3.73 (1H,m), 3.87 (1H,m), 4.84 (1H,m), 4.92 (1H,m), 6.61 (2H,d), 7.22 (6H.m), 7.36 (1H,d), 7.28 (2H,d), 7.76 (3H,ns).
20 ¹³C (dmso): 155.8, 155.7, 138.5, +129.1, +129.0, +128.0, +126.1, 122.9, +112.7, +74.6, +74.3, -72.7, -66.2, -57.2, +53.6, -49.5, -37.4, -36.7, -35.5, -32.1, -27.6, +26.2,
25 +20.0, +19.8.

Example 8

The synthesis of compound 205 from compound 198

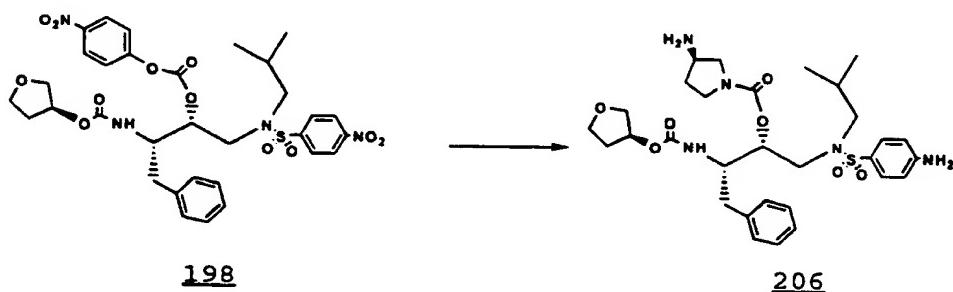
5 was carried as described in Example 1, except that 1,4-diamino-4-N-Boc-butane was used in place of di-p-nitrophenyl carbonate.

C,H,N: calc: 48.17, 5.59, 8.26, found 48.02, 5.96, 8.24
 $C_{30}H_{45}N_5O_7S_1 \cdot 2 CF_3COOH$

10 LC/MS (ES+) 620 (M+1) 1 peak at 4.36 min.

Analytical HPLC(A) $t=14.93$ min.

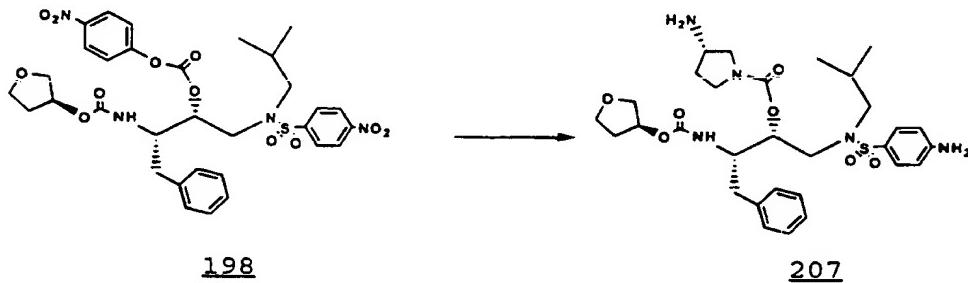
1H: d-6 DMSO: 0.77 (6H,dd), 1.43 (4H,m), 1.82 (2H,m),
 2.03 (1H,m), 2.77 (4H,m), 2.95 (3H,m), 3.31 (2H,m), 3.56
 (1H,m), 3.63 (1H,m), 3.70 (1H,bq), 3.82 (1H,m), 4.85
 15 (1H,m), 4.92 (1H,m), 6.62 (2H,d), 7.2 (7H,m), 7.38
 (2H,d), 7.72 (3H,bs).
 ^{13}C : 155.7, 152.9, +138.6, +129.1, +129.0, +128.0,
 +126.1, +123.0, +112.7, +74.4, +74.3, -72.7, -66.2, -
 57.2, +53.7, -49.7, -38.6, -38.5, -35.4, -32.1, -26.3,
 20 +26.2, -24.4, +20.1, +19.9.

Example 9

The synthesis of compound 206 from compound 198 was carried as described in Example 1, except that (3R)-(+)-3-Boc-aminopyrrolidine was used in place of di-p-nitrophenyl carbonate.

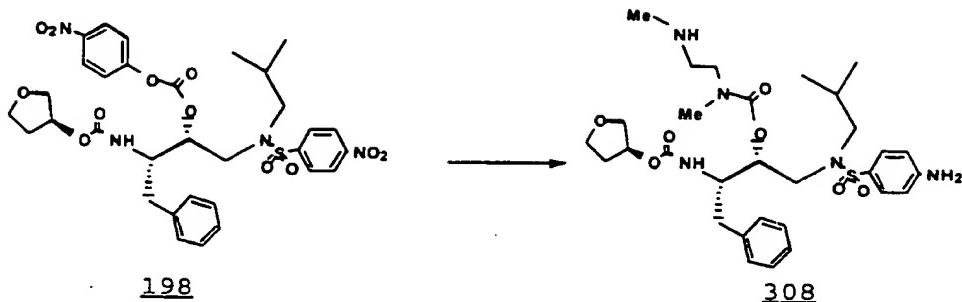
- 5 C,H,N: calc: 48.28, 5.36, 8.28, found 47.89, 5.53, 8.57
 $C_{30}H_{43}N_5O_7S_1 \times 2$ TFA
 LC/MS (ES+) 618 (M+1) 1 peak at 4.32 min.
 Analytical HPLC(A) t=14.31 min.
 1H and 13C NMR: complex and overlapping mixtures of
 10 rotomers.

Example 10



- The synthesis of compound 207 from compound 198 was carried as described in Example 1, except that (3S)-(-)-3-Boc-aminopyrrolidine was used in place of di-p-nitrophenyl carbonate.
- 15 LC/MS (ES+) 618 (M+1) 1 peak at 4.19 min.
 Analytical HPLC(A) t=14.75 min.
 20 1H and 13C NMR: complex and overlapping mixtures of rotomers.

Example 11



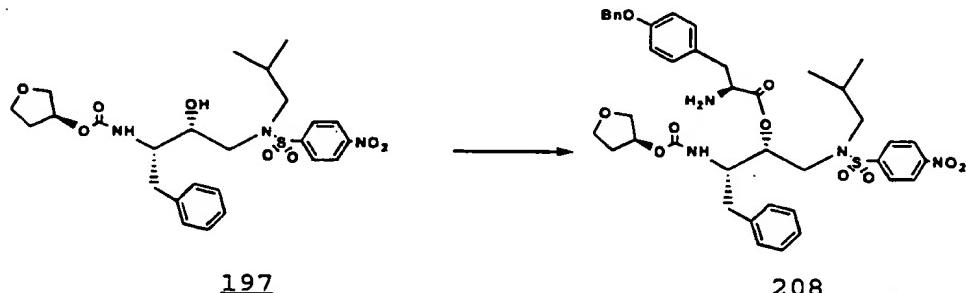
5 The synthesis of compound 308 from compound 198
was carried as described in Example 1, except that N-
triphenylmethyl-N,N'-dimethylethanediamine was used in
place of di-p-nitrophenyl carbonate.

¹H-NMR: 0.76 (6H, dd), 1.65 (2H, m), 1.95 (1H, m), 2.07
 10 (1H, m), 2.7 (2H, m), 2.75 (3H, s), 2.95 (3H, m), 3.45
 (2H, m), 3.7 (4H, m), 4.2 (2H, bm), 5.05 (2H, bd), 6.62
 (2H, d), 7.2 (5H, m), 7.5 (2H, d).
 LC/MS: 1 peak, 620 (MH⁺).

15 Example 12

General Procedures

Acylation:



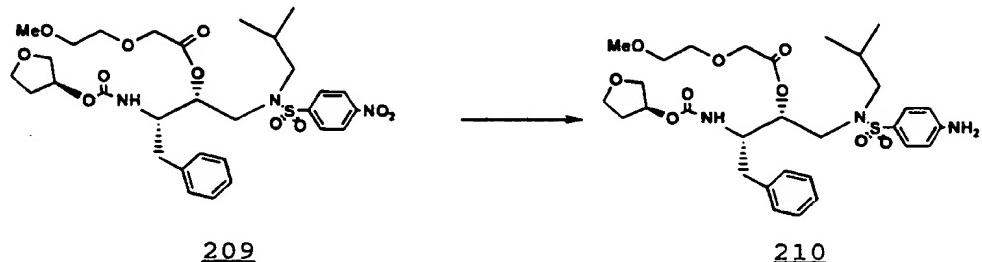
20 To 200mg (.37mM) of 197 dissolved in 5ml CH₂Cl₂, was added N-CBz-L-Benzyl tyrosine 183mg (.41mM) followed by 231 mg (1.12mM) DCC, followed by 29mg (.23mM) DMAP. The reaction is stirred at rt for 24hr. The precipitates

present were removed by filtration. The filtrate was then concentrated in vacuo. The final compound was purified on preparative reversed phase C₁₈ using purification by HPLC C₁₈ Waters Delta Prep 3000 Column:

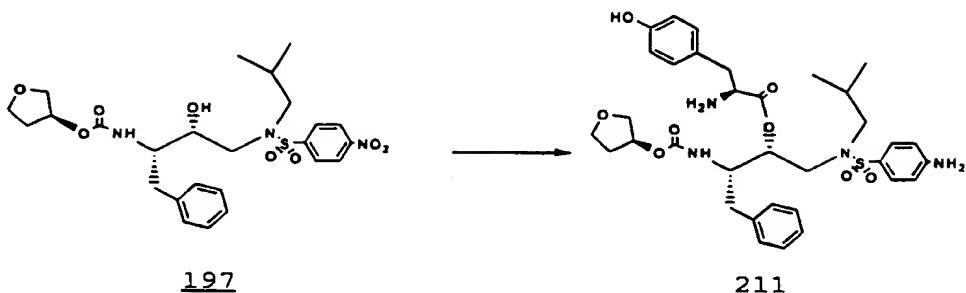
5 YMC-Pack ODS AA 12S05-2520WT 250X20 mm I.D. S-5mm, 120Å, 0-100% B over 1/2h, flow=18 ml/min, monitored at 220 nm, B=0.1% trifluoroacetic acid in acetonitrile, A=0.1% trifluoroacetic acid in water. Analytical Column: YMC-Pack ODS AA1 2S05-2520WT 250X4.6 mmI.D. S-5mm, 120Å, 0-100% B at 1.5 ml/min. over 1/2 h, monitored at 220 nm, B=0.1% trifluoroacetic acid in acetonitrile, A=0.1% trifluoroacetic acid in water.

The aqueous phase was lyophilized to give 59 mg, (16.3%) GW431896X, (U11484-72-10) t_{HPLC}=11.71 min., 15 MW=966.04, LC/MS=MH+967.

Reduction of the Nitro Functionality:



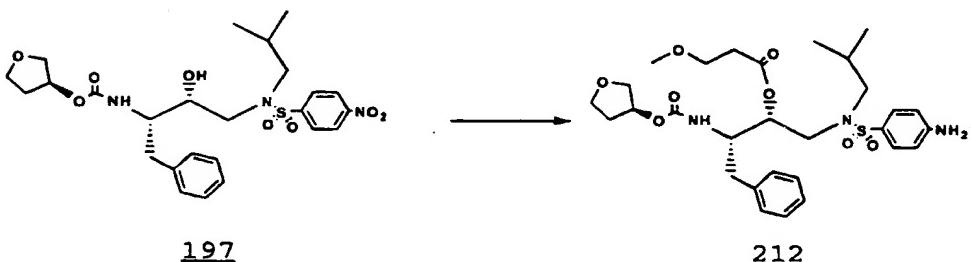
A slurry of 209 (170 mg) and 10 mg of 10% Pd.C in 95% EtOH was flushed with hydrogen in a scintillation vial equipped with septum and a stir bar. Continuous overnight hydrogenolysis under hydrogen balloon resulted in a complete conversion. The crude preparation was then filtered off the catalyst, and purified on RP C₁₈ HPLC (Prep Nova-Pack C186 um, 60 Å, gradient 0-100% B over 30 min. The desired product was collected and lyophilized affording a white fluffy solid (50 mg, 30.8%).

Example 13

Compound 211 was obtained following the

5 acylation and reduction procedures of Example 12.

ES+ 669.2 (M+1), tHPLC=8.06 min (D), ¹³C NMR (DMSO) 168.9,
156.9, 155.7, 153.1, 138.1, 130.5, 129.2, 129.1, 128.1,
126.2, 124.7, 122.5, 112.8, 76.2, 74.5, 72.5, 66.1, 58.0,
53.6, 52.6, 49.2, 33.6, 32.1, 26.6, 25.3, 20.0.
10 tHPLC=11.71 min (D), ES+ 967 (M+1).

Example 14

15 212 was obtained following the procedures of
Example 12.

tHPLC= 9.45 min (D), ES+ 592.2 (M+1).
¹³C NMR (DMSO) 171.5, 155.8, 148.9, 137.8, 129.5, 129.3,
128.5, 126.7, 115.2, 75.2, 73.8, 73.1, 68.3, 67.0, 58.7,
20 57.1, 53.3, 49.2, 35.4, 32.4, 26.7, 20.1, 19.8.
¹H(CDCI₃, 399.42 KHz): 8.33 (2H, d, J=8.8), 7.95 (2H, d,
J=8.8), 7.23 (5H, m) 5.22 (m, 2H), 5.08 (m, 1H), 4.08 (m,
1H), 3.80-3.45 (7H, m), 3.41 (3H, s), 2.98 (m, 3H), 2.66

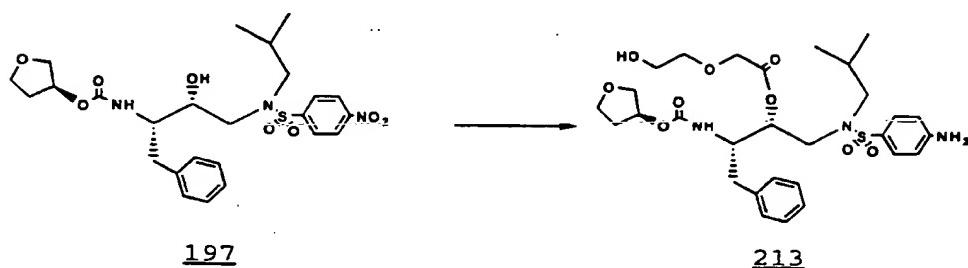
(m, 1H), 2.57 (m, 2H), 2.10 (s, 1H), 1.93 (2H, m), 0.82 (3H, d), 0.78 (3H, d).

ES+ 622 (M+1), 644 (M+Na)

tHPLC = 10.29 min (D).

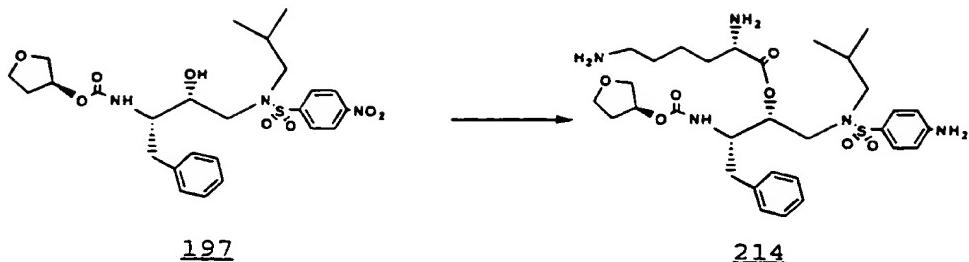
- 5 13C NMR (CDCl₃): 171.3, 155.5, 149.9, 145.6, 136.9, 129.2, 128.6, 128.5, 126.8, 124.4, 76.7, 75.3, 73.2, 72.9, 68.2, 66.9, 58.7, 55.9, 53.1, 48.3, 35.3, 32.7, 26.3, 19.9, 19.8.

10

Example 15

15 Compound 213 was obtained following the procedure of Example 12. tHPLC = 9.21 min (D); ES+ 622 (M+1).

- 16 13C NMR (CDCl₃): 170.54, 156.2, 148.6, 136.8, 129.4, 129.2, 128.6, 126.6, 115.7, 76.7, 74.6, 73.2, 71.8, 70.6, 68.2, 66.9, 58.9, 57.3, 53.8, 49.4, 36.2, 33.1, 26.8, 19.8, 19.5.
- 20 Intermediate: t HPLC = 10.05 min (D); ES+= 652 (M+H) 674 (M+Na).

Example 16

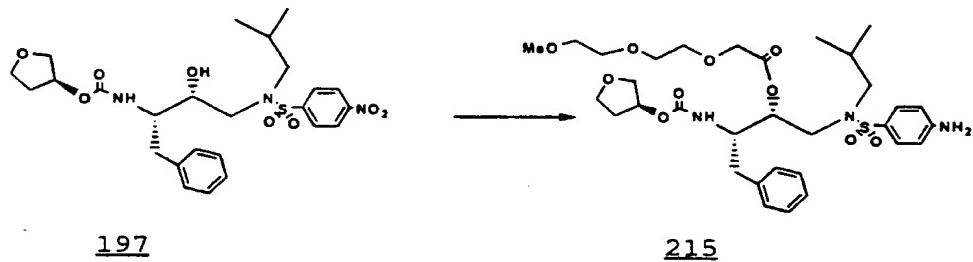
214 was obtained following the procedure of

5 Example 12.

ES+ 634.4 (M+1); t HPLC = 7.17 min (D).

13C (DMSO): 169.3, 155.8, 153.1, 138.0, 129.1, 129.0, 128.1, 126.3, 122.6, 112.8, 94.3, 75.6, 74.6, 72.4, 66.1, 57.8, 52.7, 52.0, 49.3, 38.4, 34.7, 32.2, 29.1, 26.6,

10 21.4, 20.1, 20.0.

Example 17

15 215 was obtained following the procedure of
Example 12.

t HPLC = 9.12 min (D)

1H (DMSO) all signals broad: 7.38 (3H, br m), 7.20 (5H, br m), 6.62 (2H, br m), 5.15 (1H, br m), 4.92 (1H, br m),
20 4.00 (3H, m), 3.7-3.0 (16H, m), 2.78 (2H, m), 2.57 (3H, m), 2.04 (m, 1H), 1.78 (m, 2H), 0.77 (6H, m)
13C (DMSO) 170.6, 156.3, 153.7, 139.1, 129.8, 128.4, 126.7, 123.7, 113.3, 79.8, 79.2, 77.3, 76.1, 75.4, 75.2,

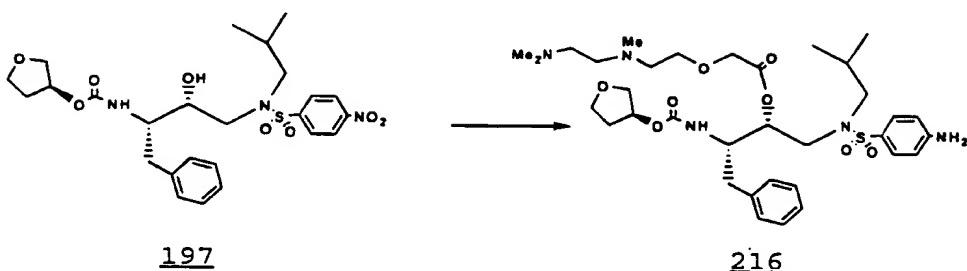
73.0, 71.9, 52.3, 51.8, 48.2, 46.7, 39.9, 38.7, 25.8,
22.6.

Intermediate:

t HPLC = 10.18 min (D); ES+ 696.3 (M+1).

5

Example 18

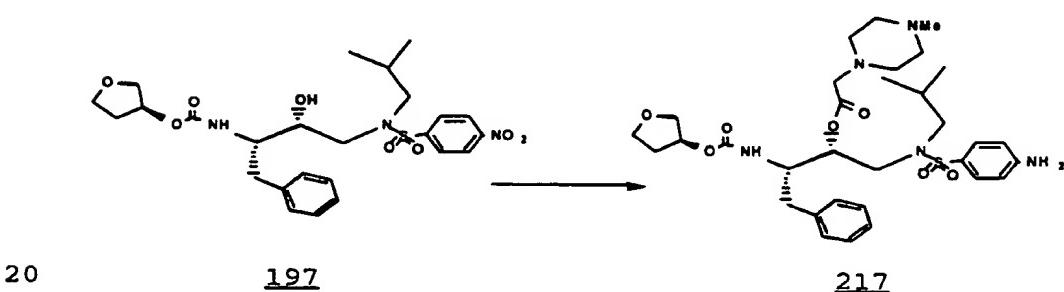


10 216 was obtained following the procedure of
Example 12.

1H-NMR: 0.97 (6H,t), 1.95 (2H,m), 2.20 (1H,m), 2.9 (2H,m), 2.96 (6H,s), 3.00 (3H,s), 3.38 (1H,m), 3.42 (3H,m), 3.36 (1H,m), 3.6 (2H,m), 3.7 (6H,m), 3.98 (2H,m), 4.2 (2H,dd), 5.1 (1H,bs), 5.4 (1H,m), 6.8 (2H,d), 7.4 (5H,m), 7.6 (2H,d).

15 LC-MS: 1 peak, 692 (MH⁺).

Example 19

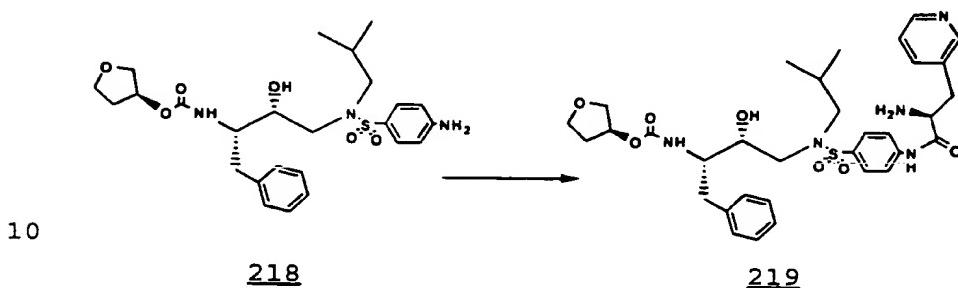


217 was obtained following the procedure of
Example 12.

1H-NMR (CDCl₃): 0.78 (6H, dd), 1.9 (2H, m), 2.1 (1H, m), 2.3 (3H, s), 2.9 (8H, m), 2.9 (2H, m), 3.15 (1H, m), 3.35 (1H, m), 3.5 (1H, m), 3.75 (4H, m), 4.06 (2H, s), 4.15 (2H, m), 4.9 (1H, dd), 5.05 (1H, bs), 5.2 (1H, bs), 6.63 (2H, d), 7.2 (5H, m), 7.55 (2H, d), 8.0 (2H, m).
 5
 ESMSP: 676 (M⁺).

Example 20

General Procedure for N-acylated Compounds



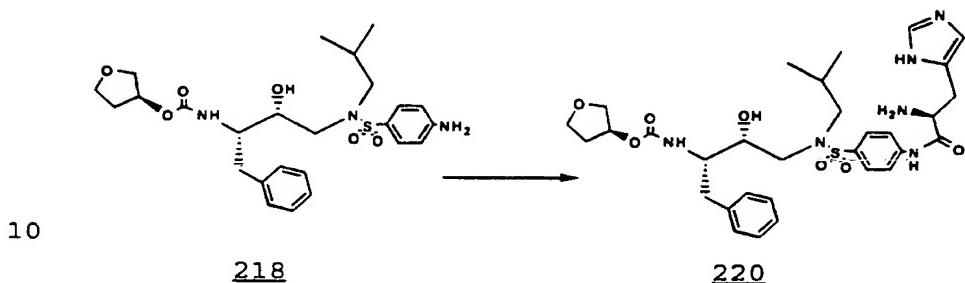
A mixture of 0.5g (1 mMol) of (3S)-Tetrahydro-3-furfuryl-N-((1S,2R)-1-benzyl-2-hydroxy-3-(N-isobutyl-4-aminobenzenesulfonamido)propyl) carbamate, 0.4g (1.5 mMol) of Boc-(S)-3-pyridyl alanine, 0.29g (1.5 mMol) EDCI and 0.1g 4-dimethylamino pyridine in 10 ml of N,N-dimethylformamide was stirred at 25° for 12 hours. The volatiles were removed in vacuo and the residue was partitioned between ethyl acetate and 1N hydrochloric acid. The organic layer was washed with 1N sodium hydroxide and brine, dried over magnesium sulfate and concentrated in vacuo. The residue was chromatographed on a 2 inch plug of silica gel (1:1 ethyl acetate: hexane) to give the desired N-acylated material.

methanol gave the desired prodrug as a white foam (0.2g, 26%).

⁵ $\text{H}_1\text{-NMR}$ (acetonitrile- D_3): 0.95 (6H, dd), 2.0 (2H, m), 2.25 (1H, m), 2.8-3.1 (5H, m), 3.6-4.0 (7H, m), 4.25 (1H, m), 4.75 (1H, m), 5.18 (1H, m), 5.45 (1H, m), 7.0 (2H, d), 7.4 (5H, m), 7.75 (2H, d), 8.2 (1H, m), 8.8 (1H, d), 8.85 (1H, d), 9.15 (1H, s).

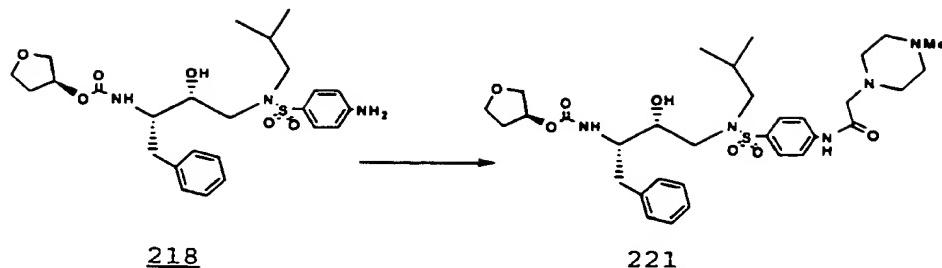
LC/MS: 1 peak, 654 (MH^+).

Example 21



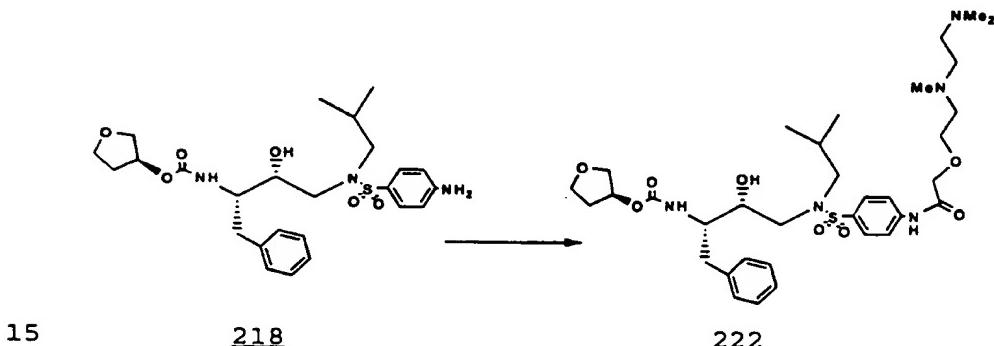
220 was obtained using the general procedure in Example 20.

15 ¹H-NMR (acetone-d₆/ methanol-d₄): 0.95 (6H, t), 2.0 (2H, m), 2.2 (1H, m), 2.90 (1H, dd), 2.95 (2H, d), 3.12 (1H, dd), 3.4 (2H, m), 6 (1H, d), 3.8 (5H, m), 4.4 (2H, bm), 6.82 (2H, d), 7.20 (1H, s), 7.4 (5H, m), 7.65 (2H, d), 8.0 (1H, s).
20 LC/MS: 1 peak, 643 (MH⁺).

Example 22

5 221 was obtained using the general procedure in
Example 20.

1H-NMR (DMSO d-6): 0.76 (6H,t), 1.80 (2H,m), 2.10 (1H,m),
3.7 (4H,m), 3.75 (3H,s), 3.2 (5H,m), 3.58 (2H,s), 3.7
(4H,m), 4.97 (1H,bs), 5.18 (1H,bs), 6.7 (2H,d), 7.22
10 (5H,m), 7.45 (2H,d).
LC/MS: 1 peak, 646 (MH+).

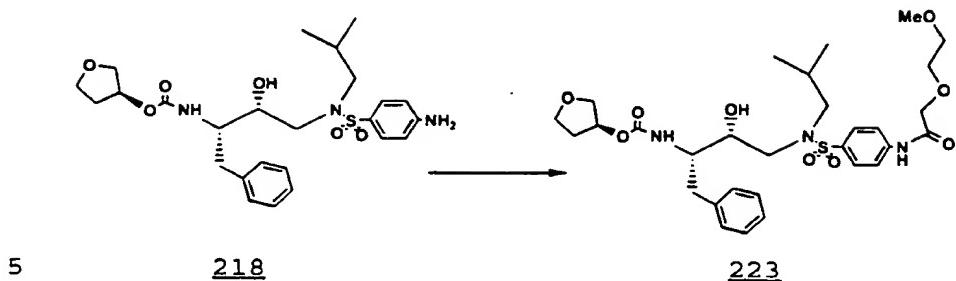
Example 23

222 was obtained using the general procedure in
Example 20.

1HNMR (acetonitrile d-3): 1.0 (6H,t), 2.0 (2H,m), 2.2
(1H,m), 3.00 (6H,s), 3.02 (3H,s), 3.1 (4H,m), 3.5 (3H,m),
20 3.8 (8H,m), 4.4 (2H,s), 5.15 (1H,bs), 7.4 (5H,m), 7.97
(2H, d), 8.04 (2H,d).

LC/MS: 1 peak, 692 (MH⁺).

Example 24

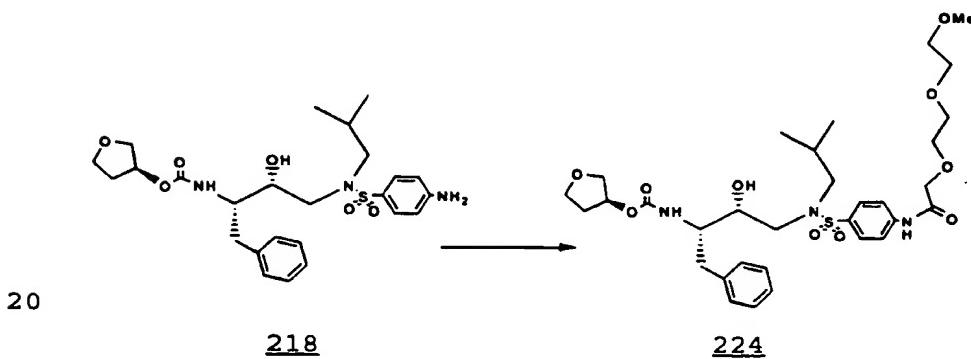


223 was obtained using the general procedure in Example 20.

t HPLC = 9.22 min (D); ES+ 622 (M+1).

¹H NMR δ₆-DMSO: 0.76 (6H, dd), 1.0-1.8 (15H, m), 2.03
10 (1H, m), 2.58 (2H, m), 2.79 (2H, m), 3.11 (1H, m), 3.28
(3H, s), 3.3-3.5 (12H, m), 3.94 (1H, m), 4.08 (1H, m), 4.94
(1H, m), 5.14 (1H, m), 6.61 (2H, d), 7.22 (5H, m), 7.40
(3H, m).
¹³C (DMSO) 169.7, 165.9, 152.9, 138.4, 129.2, 129.1,
15 128.1, 126.2, 123.1, 112.8, 74.4, 74.1, 72.5, 71.2, 69.8,
66.1, 58.1, 57.1, 52.9, 47.5, 33.4, 33.2, 26.3, 24.5,
18.9, 18.8.

Example 25

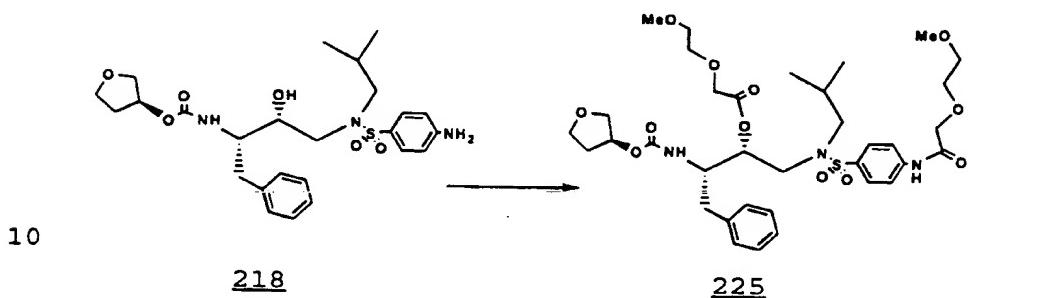


224 was obtained using the general procedure in Example 20.

Example 26

O,N-diacylated Prodrugs

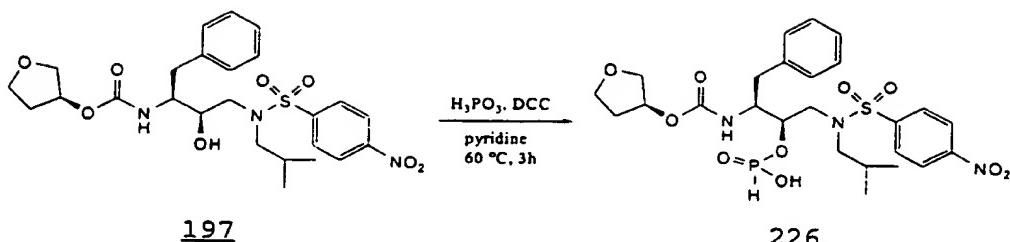
5 The general procedure for N,O-diacylated compounds followed the protocol outlined in Example 20, above, except that a five fold excess of reagents was used relative to the starting material.



10

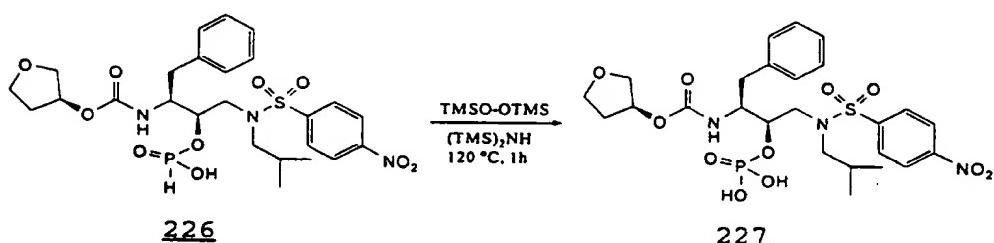
218225

t HPLC 9.26 min (D); ES+ 738 (M+1) 760 (M+Na).
¹³C (DMSO): 170.2, 169.8, 156.4, 143.4, 138.8, 129.5,
 128.8, 128.5, 126.8, 119.7, 74.9, 74.2, 73.7, 71.6, 70.7,
 15 70.3, 68.0, 67.2, 59.3, 57.6, 53.8, 49.6, 35.7, 33.8,
 27.1, 20.4.
¹H (DMSO): 10.1 (1H, s), 7.84 (d, 2H, J=8.5), 7.76 (d,
 J=8.7, 2H), 7.40 (1H, d, J=9.2), 7.22 (m, 5H), 5.14 (1H,
 m), 4.95 (1H, m), 4.1 (m, 8H), 3.7-3.3 (m, 13H), 3.28 (s,
 20 3H), 3.26 (s, 3H), 2.86 (m, 2H), 2.73 (m, 1H), 2.59 (m,
 1H), 2.04 (m, 1H), 1.83 (m, 2H), 0.78 (m, 6H).

Example 27

To a mixture of 197 (2.93 g, 5.47 mmol) and 5 phosphorous acid (Aldrich, 2.2 equiv., 12.03 mmol, 987 mg) in 20 ml pyridine was added 1,3-dicyclohexylcarbodiimide (Aldrich, 2.1 equiv., 11.49 mmol, 2.37 g) and the reaction heated to 60 °C under nitrogen for 3h. Solvent was removed *in vacuo*, the 10 residue treated with 200 ml 0.1N aqueous sodium bicarbonate and stirred 1h at ambient temperature. The mixture was filtered, the filtrate acidified to pH 1.5 by addition of conc. HCl and extracted with ethyl acetate (3 x 100 ml). The combined organic layers were dried over 15 magnesium sulfate, filtered and concentrated *in vacuo* to give 3.15g (96%) of desired product 226 which was used directly in the next reaction. HPLC: Rt = 8.91 min (96%), MS (AP+) 600.5 (M+1).

20

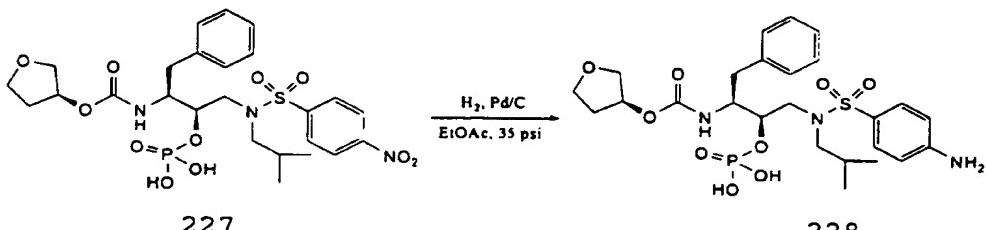
Example 28

A suspension of 226 (~5.47 mmol) in 18 ml hexamethyldisilazane was stirred at 120°C until homogeneous followed by addition of bis(trimethylsilyl) peroxide (Gelest, Inc., 2.3 equiv., 12.58 mmol, 2.24 g, 5 2.71 ml). After 1h the mixture was cooled to ambient temperature, solvent removed in vacuo, the residue stirred with 100 ml methanol, solvent removed in vacuo, the residue stirred with 100 ml 0.1N aqueous sodium bicarbonate, acidified to pH 1.5 by addition of conc. 10 HCl, saturated with brine and extracted with ethyl acetate (3 x 100 ml). The combined organic layers were dried over magnesium sulfate, filtered and concentrated in vacuo to give 2.98 g (88%) of desired product 227, which was used directly in the next reaction. HPLC: Rt = 15 9.28 min (90%), MS (AP+) 616.5 (M+1).

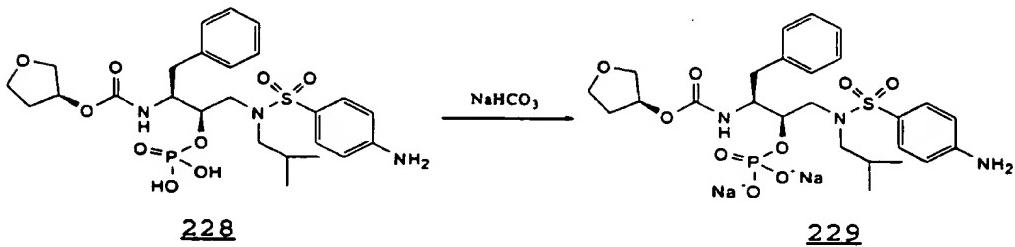
Alternatively, 227 can be synthesized directly from 197. In this method, 197 was dissolved in pyridine (300mL). The resulting solution was concentrated in vacuo to about 150 ml at 50-55°C. The solution was then 20 cooled under N₂ to 5°C, and treated with POCl₃ (6.5 ml, 1.24 equiv.) over 2 minutes. The cooling bath was removed and the reaction stirred at ambient temperature for 2.5 hrs. The solution was then cooled to 5°C and water (300 ml) was added over 30 minutes.

25 The resulting mixture was extracted with 4-methylpentan-2-one (MIBK, 2 x 150 ml). The combined extracts were washed with 2N HCl (2 x 250 ml). The acid washes were back extracted with MIBK (60 ml), then the combined MIBK solutions were treated with 2N HCl (150 30 ml). The two phase mixture was stirred rapidly and heated to 50°C for 2 hours. The reaction mixture was cooled to 20°C, the phases were separated and the MIBK

solution was washed with brine (150 ml). The product, 227, was isolated by drying the solution with magnesium sulfate, filtering of the drying agent and concentrating in vacuo at 40°C to give the product as a pale yellow foam
 5 (31 g, 90% yield).

Example 29

A solution of 227 (2.98 g, 4.84 mmol) in 50 ml
 10 ethyl acetate was treated with 10% palladium on carbon
 (Aldrich, 300 mg) and put under 35 psi of hydrogen on a
 Parr shaker for 15h. Catalyst was removed by filtration
 and solvent removed in vacuo to give 2.66 g (94%) of
 desired product 228. HPLC: Rt = 7.23 min (92%), MS (ES+)
 15 586.3 (M+1).

Example 30

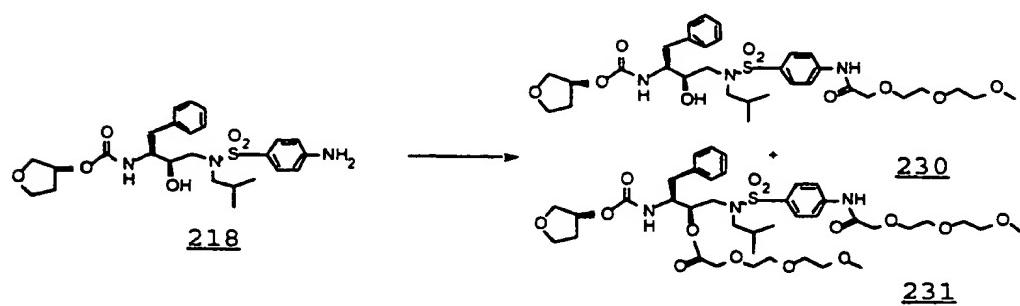
Solid 228 (2.66 g, 4.54 mmol) was treated with
 20 10 ml aqueous sodium bicarbonate (Baker, 3.0 equiv.,
 13.63 mmol, 1.14 g) and loaded onto a resin column
 (Mitsubishi Kasei Corp., MCI-gel, CHP-20). Distilled
 water was run through until the eluent was neutral
 25 followed by product elution with 1% acetonitrile in

water. Pure fractions were pooled and lyophilized to give 918 mg of pure bis-sodium salt 229.

Alternatively, 7 g of 228 was dissolved in 100 ml of EtOAc with warming and the solution was extracted 5 with 100 ml of aqueous 250 mM triethylammonium bicarbonate (TEABC) (2X). The aqueous extracts were combined and diluted to 1500 ml with water. This solution was applied to a 300 ml DEAE-52 column (Whatman) which was equilibrated with 50 mM TEABC. The column was 10 washed with 8 L of 50 mM TEABC and the TEA salt was eluted with 2 L of 250 mM TEABC. The solution was evaporated en vacuo to 100 ml then lyophilized to yield the TEA salt (1.5 TEA equivalents). The TEA salt was (5.8 g) was dissolved in 200 ml water, 300 ml of 1 N HCl 15 was added and the mixture was extracted with EtOAc (3 x 200 ml). The ethyl acetate solution was dried with MgSO₄ then evaporated en vacuo to yield 4 g of the free acid. Two grams of the free acid was dissolved in 50 ml of acetonitrile and a solution of 573 mg NaHCO₃ in 200 ml 20 water was added. The mixture was lyophilized yielding 2.1 g of the bis sodium salt (compound 229).

Example 31

25



0.53 g (3.0 mmol) 2-[2-(2-Methoxyethoxy)ethoxy] acetic acid was added to a stirred solution of 1.2 g

(3.15 mmol) HATU 0.2 g (1.47 mmol) HOAT 0.4 g (4.0 mmol) NMM in 10 ml anhydrous N,N-dimethylformamide. The mixture was stirred at room temperature for 30 minutes, then 0.5 g (1 mmol) of (3S)-Tetrahydro-3-furfuryl-N-((1S,2R)-1-benzyl-2hydroxy-3-(N-isobutyl-4-aminobenzenesulfonamido)-propyl) carbamate was added to the solution in one portion. The mixture was stirred at 20°C for an hour then at 50°C for an additional 12 hours. It was then cooled to 20°C, 50 ml of ether was added, and the solution was washed with water three times. The aqueous phase was washed with ether, and then the combined organic phases were dried with anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel chromatography to obtain the desired Mono-(N) acylated (102 mg, 15 %) and Bis-(O,N) acylated (262 mg, 32%) compounds.

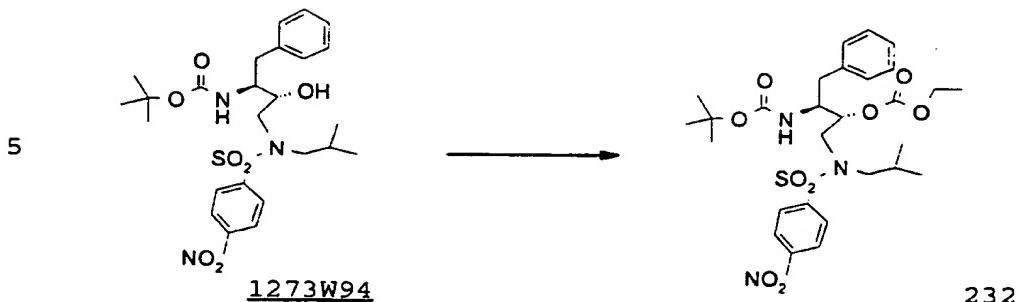
Mono-(N)-acylated: 1H-NMR(CDC13): 0.85 (dd, 6H), 1.85 (m, 2H), 2.08 (m, 1H), 2.8-3.1 (m, 7H), 3.33 (s, 3H), 3.55 (m, 3H), 3.70-3.90 (m, 8H), 4.1 (s, 2H), 5.0 (d, 1H), 5.08 (s(br), 1H), 7.2 (m, 5H), 7.70 (d, 2H), 7.80 (d, 2H), 9.09 (s, 1H).

MS(FAB+): 666 (M+1).

Bis-(O,N)-acylated: 1H-NMR(CDC13): 0.77 (m, 6H), 1.81 (m, 1H), 1.95 (m, 1H), 2.05 (m, 1H), 2.6-3.0 (m, 6H), 3.2 (m, 1H), 3.332 (s, 3H), 3.338 (s, 3H), 3.5-3.8 (m, 18H), 4.1 (s, 2H), 4.14 (s, 2H), 4.17 (m, 1H), 5.05 (m, 2H), 5.25 (s(br), 1H), 7.2 (m, 5H), 7.69 (d, 2H), 7.78 (d, 2H), 9.06 (s, 1H).

MS(FAB+): 826 (M+1), 848 (M+Na).

Example 32



We dissolved 0.521g (1 mM) of 1273W94 in 5 ml
10 THF, then cooled to -78°C under nitrogen, and added 1.56
ml (2.5 mM) of a 1.6 M solution of nBuLi in hexane.
After 20 min at -78°C, we added 105 µL (1.1 mM) of ethyl
chlorocarbamate and warmed up the reaction to room
temperature, followed by addition of another 105 µL of
15 ethyl chlorocarbamate.

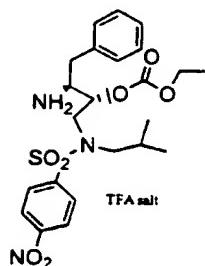
After stirring for additional 4 hrs, the reaction was quenched with water and the organic solvent evaporated. Part of the crude product was purified on a silica gel ($R_f = 0.69$ (1:2 ethyl acetate:hexane)), yielding 0.131g of the product.

$C_{23}H_{33}N_5O_5S_1$. 2.2 TFA

LC/MS (ES+) 594 (M+1) 1 peak at 6.96 min.

Analytical HPLC (A) t=24.57 min

25 13C (CDC13): 155.8, 154.4, 149.9, 145.7, 136.8, +129.2,
+128.7, +126.8, +124.2, 80.1, +76.9, -64.3, -56.2, -52.5,
-48.7, -36.2, +28.1, +26.4, +20.0, +19.8, +14.3.

Example 33233

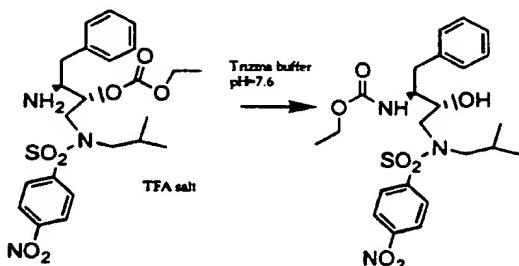
We dissolved 0.131g of the above ethyl carbonate in 4 ml DCM, followed by 4 ml of TFA. Solvents were then removed after 45 min at room temperature, resulting in the title compound.

¹H (DMSO): 8.37 (2H, d, J=7.2), 8.15 (2H, m), 8.00 (2H, d, J=7.0), 7.37 (5H, m), 5.04 (1H, d, J=6.9), 4.06 (2H, q, J=7.0), 3.82 ((1H, m), 3.35 (2H, m), 2.95 (4H, m), 1.82 (1H, m), 1.20 (3H, t, J=7.0), 0.72 (overlapping doublets, 6H, J=6.2).

LC/MS 1 peak at 4.76 min.

ES+ 497.3 (M+1).

15

Example 34O,N-Acyloxy Rearrangement233234

20 C, H, N: calc: 53.26, 6.14, 7.57, found 53.22, 6.14, 7.57
 $C_{23}H_{33}N_5O_5S_1 \times 0.8$ TFA

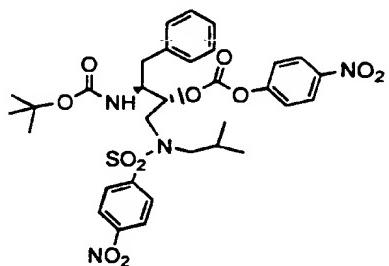
LC/MS (ES+) 594 (M+1) 1 peak at 6.96 min.

Analytical HPLC(A) t=24.57 min.

1H (DMSO): 8.34 (2H, d, J=8.7), 8.02 (2H, d, J=8.0), 7.19
5 (5H, m), 6.98 (1H, d, J=7.2), 5.00 (1H, m), 3.83 (2H, q),
3.50 (2H, m), 3.06 (m, 2H), 2.96 (2H, m), 2.43 (1H, m),
1.97 (1H, m), 1.02 (3H, t), 0.84 (3H, d), 0.82 (3H, d).
13C (DMSO): 156.2, 150.1, 145.7, 140.0, +129.7, +129.2,
+128.5, +126.3, +125.0, +71.8, -60.0, +56.2, -56.0,
-51.8, -36.0, +26.3, +20.3, +20.1, +14.6.

10

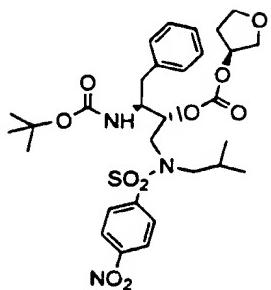
Example 35



235

Synthesis of 235 was accomplished analogous to
15 that set forth in Example 1.

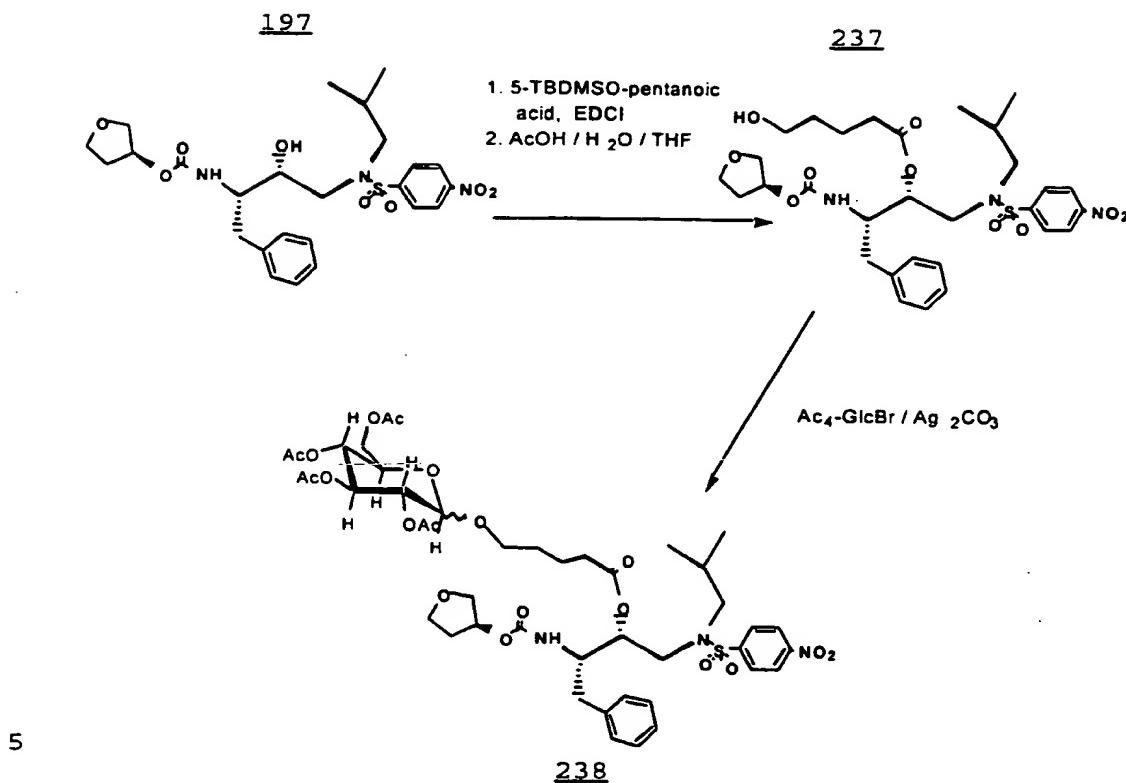
Yield 15.2%; tHPLC=25.2 min (A).
Rf=0.54 (B); ES+ 687.3 (M+1).
1H (CDCl3): 8.34 (overlapping d+d, 4H), 7.97 (d, 2H,
J=8.9), 7.35 (7H, m), 5.09 (1H, m), 4.56 (1H, d, J=8.4),
20 4.20 (1H, m), 3.54 (1H, m), 3.00 (3H, m), 2.82 (1H, m),
1.84 (1H, m), 1.37 (9H, s), 0.84 (3H, d), 0.82 (3H, d).

Example 36236

We dissolved 150 mg of 235 in 3 ml of anhydrous dioxane, added 0.35 ml of S(+)-3-OH-THF and 0.14 ml triethyl amine. The mixture was refluxed gently under nitrogen for 2 days. Conversion to 236 was quantitative. Solvents were removed and the compound purified on silica (B).

tHPLC=22.98 min (A); ES+ 636.2 (M+1).
1H NMR (CDCl₃): 8.29 (2H, d), 7.91 (2H, d), 7.22 (5H, m), 5.13 (1H, m), 4.96 (1H, m), 4.52 (1H, d), 4.02 (1H, m), 3.84 (2H, m), 3.44 (1H, m), 3.36 (1H, m), 3.10 (3H, m, overlap), 2.88 (2H, m), 2.64 (1H, m), 2.14 (1H, m), 2.05 (1H, m), 1.84 (1H, m), 1.27 (9H, s), 0.78 (6H, two overl. d).

Example 37
Carbohydrate-Based Prodrugs



A mixture of 0.54g (1 mMol) of (3S)-Tetrahydro-3-furfuryl-N-((1S,2R)-1-benzyl-2-hydroxy-3-(N-isobutyl-4-aminobenzenesulfonamido)propyl) carbamate, 0.46g (2 mMol) of 5-dimethyl-tert-butylosilyloxy pentanoic acid, 0.346g (1.8mMol) of EDCI and 0.556mL (4 mMol) of triethylamine in 10 ml of dimethyl formamide was stirred at rt for 24h. Another 3 mMol each of acid, EDCI and triethylamine were added and stirring was continued for an additional 96h.

10 A third batch of acid and EDCI was added (3 mMol each) and the mixture was stirred 72h to complete the reaction.

15 The reaction mixture was then diluted with ethyl acetate and extracted with 1N hydrochloric acid,

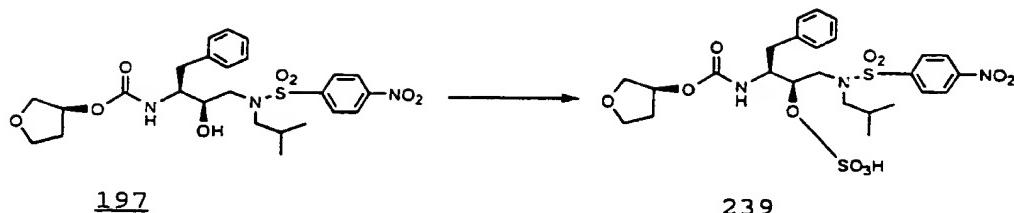
saturated sodium bicarbonate and water. Evaporation of the solvent and purification on silica gel (30% ethyl acetate-hexane) gave the desired product (500mg) as a waxy solid.

- 5 LCMS: 1 peak, 772.5 (M+Na)
1H NMR (CDCl₃): 0.01 (6H,s), 0.78 (6H,dd), 0.95 (9H,s),
1.4-1.8 (6H,m), 1.9 (2H,m), 2.05 (1H,m), 2.3 (2H,m), 2.65
(1H,m), 2.95 (2H,m), 3.22 (1H,m), 3.4 (1H,m), 3.6 (2H,m),
3.75 (3H,m), 4.8 (1H,d), 5.1 (1H,bs), 5.2 (1H,bs), 7.2
10 (5H,m), 7.95 (2H,d), 8.36 (2H,d).

450mg of the 238 was dissolved in 30 ml of tetrahydrofuran and treated with 20 ml of water and 50 ml of acetic acid. The mixture was stirred at rt for 2h and evaporated. Titration with hexane gave the desired
15 alcohol (290mg) as a white solid.

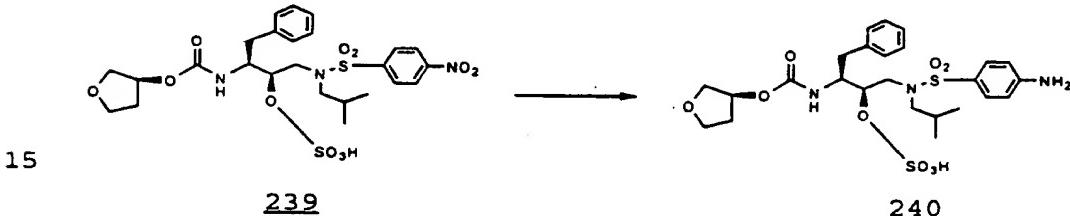
A mixture of 0.15g (0.24 mMol) of the alcohol produced above from the previous reaction, 0.205g (0.5 mMol) of tetraacetylglucosylbromide and 0.191g (0.7 mMol) of silver carbonate in 3 ml of dichloromethane was
20 stirred at rt for 6h. 150mg of additional glucosyl bromide and 150 mg of silver carbonate were added and the mixture was stirred at rt overnight. The mixture was loaded onto a pad of silica gel and eluted with 30% ethylacetate-hexane to afford the desired protected
25 carbohydrate pro-drug as a white foam (200mg).

LCMS: 1 peak, 966 (M+H).
1H-NMR (CDCl₃): 0.78 (6H,dd), 1.9 (2H,m), 2.00 (3H,s),
2.02 (3H,s), 2.05 (3H,s), 2.06 (3H,s), 2.1 (2H,m), 2.3
(2H,m), 2.7 (1H,m), 2.94 (3H,bs), 3.35 (2H,m), 3.45
30 (2H.m), 3.8 (5H,m), 4.1 (3H,m), 4.5 (1H,d), 4.9 (1H,bs),
4.95 (1H,t,), 5.08 (4H,m), 2H,d), 8.35 (2H,d).

Example 38

1.5 g (9.4 mmol) SO₃.py complex was added to a
 5 stirred solution of 1 g (1.87 mmol) of 197 in 25 mL
 anhydrous tetrahydrofuran. The mixture was stirred at
 20°C for 12 hours, then filtered. The filtrate was
 concentrated at reduced pressure, and the residue was
 transferred to a silica gel column and eluted with EtOAc
 10 (neat), followed by EtOAc:EtOH (4:1) to obtain 471 mg (47
 %) 239 as a colorless foam.

¹H-NMR (CDCl₃): 0.80 (m, 6H), 1.8-2.1 (m, 3H), 4.15
 (s(br), 1H), 4.8 (t, 1H), 5.04 (s (br), 1H).
 MS (ES-): 614 (M-1).



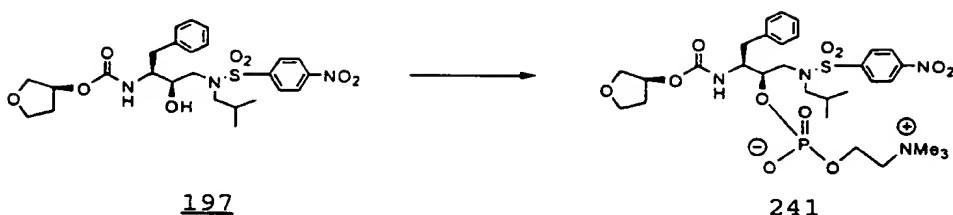
100 mg (0.162 mmol) 239 dissolved in 15 ml
 anhydrous tetrahydrofuran and 200 mg Pd/BaSO₄ (5%) was
 added to the solution. The mixture was stirred under
 20 atmospheric pressure of hydrogen for 8 hours, and then
 the catalyst was filtered. The filtrate was concentrated
 under reduced pressure then dried under vacuum (~1 Hg mm,
 48 hrs.) to produce 80 mg (81 %) 240 as a colorless foam.
¹H-NMR (DMSO-d₆): 0.85 (dd, 6H), 0.90 (m, 1H), 2.05 (m,
 25 2H), 2.58 (m, 3H), 2.84 (dd, 1H), 3.05 (m, 2H), 3.55-3.80
 (m, 6H), 4.20 (t, 1H), 4.42 (m, 1H), 4.93 (s(br), 1H),

6.09 (s, 2H), 6.70 (d, 2H), 6.80 (d, 1H), 7.15-7.40 (m, 4H), 7.51 (d, 2H).

MS (ES-) : 584 (M-1) .

5

Example 39



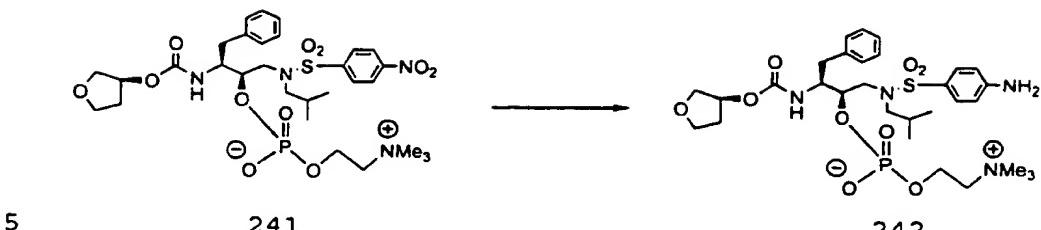
780 mg (3 mmol) 2-Chloro-1,3,2-dioxaphospholane was added to a stirred solution of 1.07 g (2 mmol) 197 10 and 0.7 ml (4 mmol) N,N-Diisopropylethylamine in 25 ml dichloromethane at 0°C. The mixture was allowed to warm up to room temperature and it was stirred for 2 hours. The mixture was then cooled to 0°C and 1.5 g (9.3 mmol) bromine was added in 5 ml dichloromethane. The mixture 15 was stirred for 1 hour at 20°C, followed by evaporation under reduced pressure. An aqueous solution (50%) of 15 ml trimethylamine was added to the residue, and the mixture was stirred at 20 °C for 12 hours.

Solvents were removed under reduced pressure 20 and 50 ml EtOAc:EtOH (9:1) was added to the residue. The solid was filtered, washed with EtOAc:EtOH (9:1) then the filtrate was concentrated under reduced pressure. The residue was chromatographed on a 3 inch plug of silica gel using ethyl acetate (neat), then methanol (neat), as 25 eluents to obtain 1.15 g (82 %) 241 as an off-white solid.

1H-NMR (CDCl₃) : 0.60 (dd, 6H), 1.70 (m, 1H), 1.95 (m, 1H), 2.10 (m, 1H), 2.8-3.2 (m, 6H), 3.4 (s (br), 9H), 5.09 (s(br), 1H), 7.25 (m, 5H), 7.83 (d, 2H), 8.28 (d, 2H) .

MS (ES+): 701 (M+1), 184 (phosphatidyl choline+).

Example 40



5

241

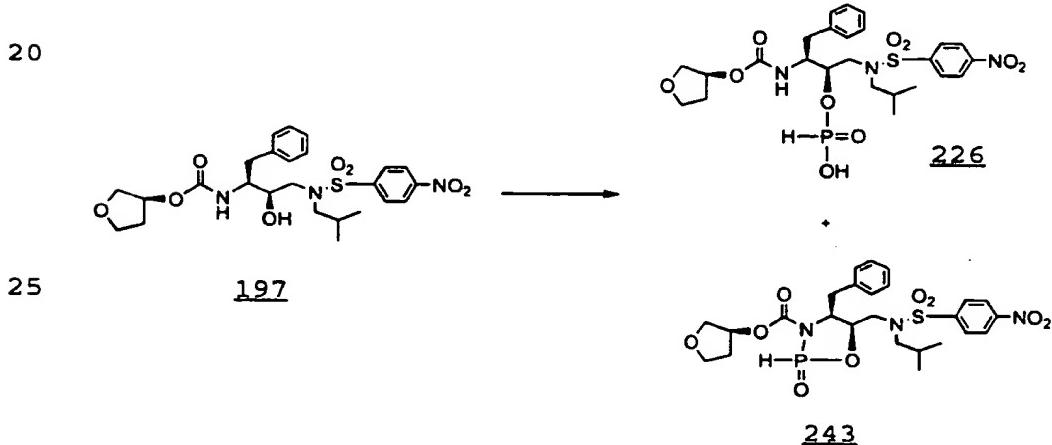
242

10 filtrate was concentrated under reduced pressure. The residue was then dissolved in 10 ml water and lyophilized to obtain 174 mg (74 %) 242 as white solid.

¹H-NMR (DMSO-d₆): 0.82 (dd, 6H), 1.80-2.00 (m, 2H), 2.10
 (m, 1H), 2.80 (m, 3H), 3.00 (m, 2H), 3.2 (s (br), 9H),
 15 4.0-4.3 (m, 4H), 4.91 (s(br), 1H), 6.08 (s(br), 2H),
 6.67 (d, 2H), 7.30 (m, 5H), 7.48 (d, 2H), 8.12 (d, 1H).

MS (ES+): 671 (M+1), 184 (phosphatidyl choline+).

Example 41



0.175 ml (2 mmol) phosphorus trichloride was added to a stirred solution of 1.07 g (2 mmol) 197 and 0.35 ml (2 mmol) N,N-Diisopropylethylamine in 25 ml dichloromethane at 20°C. The mixture was stirred for 4 hours at 20°C, then 1 ml water was added and stirred for an additional 12 hours at 20°C. 3 g anhydrous magnesium sulfate was added to the mixture and it was stirred for 30 minutes, then filtered. The filtrate was concentrated under reduced pressure and purified by silica gel chromatography using EtOAc:Hexane (4:1), then EtOAc:EtOH (1:1), to obtain 402 mg (48%) 226 and 427 mg (36%) 243.

226:

¹H-NMR (DMSO-d₆): 0.82 (dd, 6H), 1.84 (m, 1H), 1.98 (m, 1H), 2.10 (m, 1H), 2.68 (dd, 1H), 2.9-3.2 (m, 4H), 3.6-15 3.8 (m, 3H), 3.94 (t, 1H), 4.30, (s(br), 1H), 4.97 (s(br), 1H), 7.30 (m, 5H), 8.14 (d, 2H), 8.43 (d, 2H). MS(ES-): 598 (M-1).

243: (1:1 mix of diastereomers):

¹H-NMR (CDCl₃): 0.80 (m, 6H), 1.8-2.1 (m, 4H), 2.8-3.2 (m, 6H), 3.7-3.9 (m, 4H), 4.15 (m, 1H), 4.8-5.15 (m, 2H), 5.57, 5.72 ((d,d), 1H), 7.25 (m, 5H), 7.95 (dd, 2H), 8.35 (m, 2H).

MS(ES-): 580 (M-1), 598 ((M+H₂O)-1).

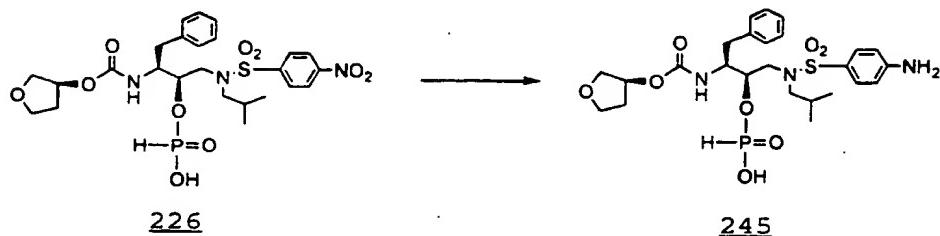
25

Example 42243244

The reduction was carried out as described in Example 40; (Yield: 79%).

1H-NMR (DMSO-d₆): 0.81 (dd, 6H), 1.82 (m, 1H), 1.95 (m, 1H), 2.08 (m, 1H), 2.6-3.15 (m, 6H), 3.6-3.75 (m, 3H), 4.03 (t, 1H), 4.28, (m, 1H), 4.96 (s(br), 1H), 6.07 (s, 2H), 6.65 (d, 2H), 7.25 (m, 5H), 7.42 (d, 2H).
 5 MS(ES-): 568 (M-1)

Example 43



10 The reduction was carried out as described in
Example 40; (Yield: 98 %).

(1:1 mix of diastereomers):

1H-NMR (DMSO- d_6): 0.82 (m, 6H), 1.75-2.0 (m, 2H), 2.05 (m, 1H), 2.6-3.2 (m, 6H), 3.55-3.8 (m, 4H), 4.02, 4.22 (m, t, 1H), 4.75 (m, 1H), 4.90, 5.01 ((d,d), 1H), 6.12 (s, 1H), 7.10 (s, 1H).

MS (ESI⁻) m/z 556 (M-1), 530 (M-15); λ_{max}

Figure 1

20 Pharmacokinetics In Sprague-Dawley Rats
Following Single Oral Dose

In order to study the pharmacokinetics of the prodrugs of this invention, we administered single oral doses of a series of prodrugs of this invention, as well as VX-478, to male and female Sprague-Dawley rats. Administration of molar equivalents of a series of prodrugs of this invention in a variety of pharmaceutical vehicles was tested.

Separate groups of male and female Sprague-Dawley rats (3/sex/group) received oral doses of compound 229 by oral gavage, in different vehicles at the same dose equivalent (40 mg/kg molar equivalent of VX-478).

- 5 The different vehicles for compound 229 were: 1) water; 2) 5/4/1; 3) PEG 400; 4) TPGS/PEG 400; and 5) PEG. The vehicles for VX-478 were: 1) 33% TPGS/PEG400/PEG; and 2) 12.5 % TPGS/PEG 400/PEG.

Blood samples were collected following 10 administration at various time intervals and analyzed for the presence of both compound 229 and its metabolite, VX-478, by HPLC and MS methods. The results of this study are tabulated below (Table IV).

TABLE IV

15

Compound	229	229	229	229	VX-478	VX-478
vehicle	H ₂ O	H ₂ O:PG:EtOH 5:4:1	PEG 400	TPGS/PEG 400/PG	33% TPGS/ PEG 400/ PG	12.5% TPGS/ PEG 400/PG
number of rats	3	3	3	3	6	13
Molar equiv. dose/ 478 Dose (mg/Kg)	40 PO	40 PO	40 PO	40 PO	41 PO	50 PO
AUC (ug*hr/ml)	11.7± 4.8	10.6 ± 7.4	7.4 ± 1.8	8.2 ± 1.6	29.6 ± 5.8	16.2 ± 1.8
Cmax (µM)	7.1± 1.7	3.3 ± 0.6	3.1 ± 0.3	3.0 ± 0.7	14.0 ± 2.2	6.0 ± 1.0
half life (hr)	1.7*	3.4*	2.8*	2.8*	2.5± 0.9	2.2± 1.0
Relative Avail. of VX-478	39.5† 90.2††	35.8† 81.8††	25.0† 57.1††	27.7† 63.3††	reference	reference

- a dose of 50 mg / Kg of compound 229 is equal to 40 mg/ Kg of VX-478.
- no compound 229 was detected in plasma at 15 min. (first data point).

* Represents the harmonic mean

20 † Relative availability of VX-478 when compared to a prototype clinical formulation

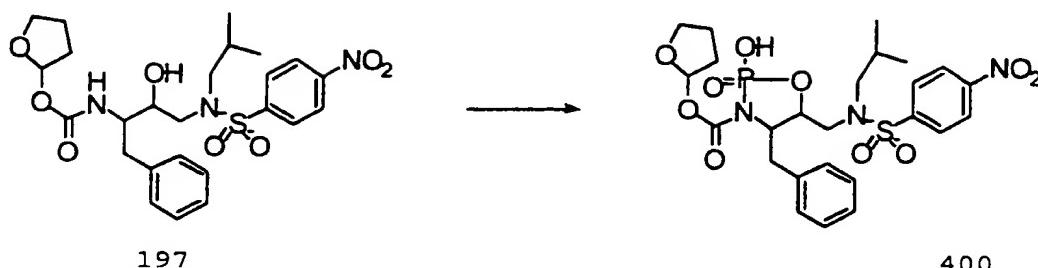
†† Relative availability of VX-478 when compared to a prototype toxicology formulation

We performed a similar study on dogs using both a solid capsule formulation of compound 229 and an ethanolic/methyl cellulose solution formulation, as compared to a TPGS-containing solution formulation of VX-478. The results from this study are presented below in Table V.

TABLE V

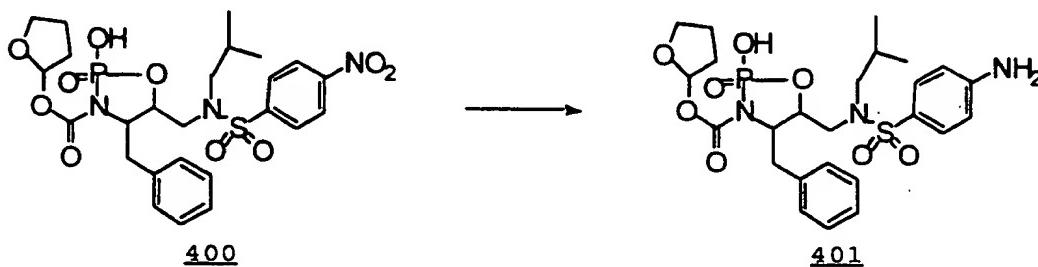
Compound	229	229	VX-478
vehicle	solid capsule	methyl cellulose in 5% EtOH/water	22% TPGS/PEG 400/PG
number of dogs	2	2	>2
Molar equiv. dose/ 478 Dose (mg/Kg)	17 PO	17 PO	17 PO
AUC (ug*hr/ml)	16.7 ± 2.7	14.2 ± 3.2	23.5 ± 7.4
Cmax (μg/ml)	6.1 ± 1.7	6.3 ± 0.3	6.8 ± 1.1
Tmax (hr)	2.3 ± 0.6	0.5 ± 0.5	1.0 ± 0.8
Relative Avail. of VX-478 (%)	71.1	60.4	reference

The results demonstrate that oral administration of compound 229 as an aqueous solution resulted in improved bioavailability in comparison to the other vehicles studied. Also, following administration of compound 229, none of that compound was detected in the first time point blood sample (or later samples), suggesting first pass metabolism to VX-478. Comparison of the aqueous dose of compound 229 with the two non-aqueous formulations used for VX-478 indicated equivalence in delivery as illustrated by the range found for the bioavailability.

Example 45

5 We added 0.28 ml (3.0 mmol) POCl₃, to a stirred solution of 1.07 g (2.0 mmol) of compound 197 in 10 ml anhydrous pyridine at 5°C. The mixture was allowed to warm up to room temperature and stirred at 20°C for 3 hours. The mixture was cooled to 0°C, and quenched with
10 10 ml water. The solvents were removed under reduced pressure, the residue was dissolved in 100 ml ethyl acetate and washed with 20 ml 1M sodium bicarbonate solution. The organic phase was dried with anhydrous magnesium sulfate, filtered then concentrated.
15 Chromatographic purification (SiO₂, EtOAc) produce 280 mg of compound 400 (Yield = 23%).

1H-NMR (DMSO-d₆): 0.86 (dd, 6H), 2.05 (m, 2H), 2.84 (d, 2H), 2.95 (dd, 1H), 3.06 (m, 1H), 3.25 (dd, 1H), 3.50-3.70
20 (m, 4H), 4.20 (m, 1H), 4.35 (m, 1H), 7.2-7.4 (m, 5H), 7.9-8.1 (m, 2H), 8.40 (m, 2H).
MS (ES-): 596 (M-1).



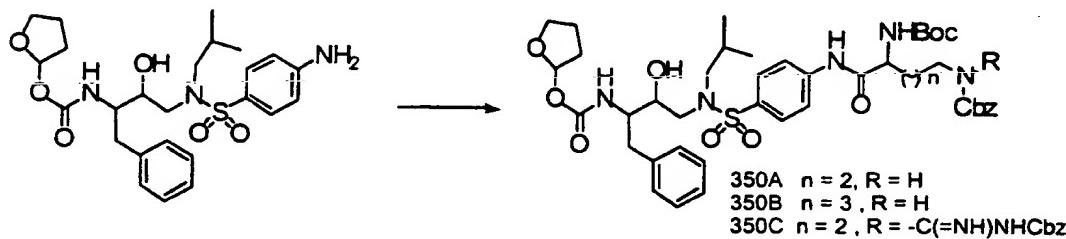
Compound 400 was converted to compound 401 using the standard hydrogenation method described above employing H₂/PdC(10%), atmospheric pressure, 4 hours at room temperature, solvent: MeOH-H₂O(5:1). Yield of 401 = 5 68%.

1H-NMR(DMSO-d₆): 0.85 (dd, 6H), 2.0 (m, 2H), 2.6-3.1 (m, 4H), 4.15 (m, 1H), 4.40 (m, 1H), 6.1 (s (br), 1H), 6.61 m (2H), 7.2-7.5 (m, 7H).

MS (ES-) : 566 (M-1).

10

Example 46



We added 1.0 g (2.8) mmol Na-t-Boc-nd-Cbz-L-15 Ornithine was added to stirred solution of 1.2 g (3.15 mmol) HATU, 0.2 g (1.47 mmol) HOAt, 0.4 g (4.0 mmol) NMM in 10 ml DMF. The mixture was stirred at room temperature for 2 hrs. then 0.5 g (1.0 mmol) of compound 218 was added and the solution was stirred at 50°C for 12 20 hours. The mixture was cooled to room temperature, 100 ml ether was added and extracted with 5x 50 ml water. The organic phase was dried with anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel 25 chromatography (Hexane-EtOAc (1:1) then EtOAc (neat)) to yield 410 mg (48%) of compound 350.

Compound 350 A

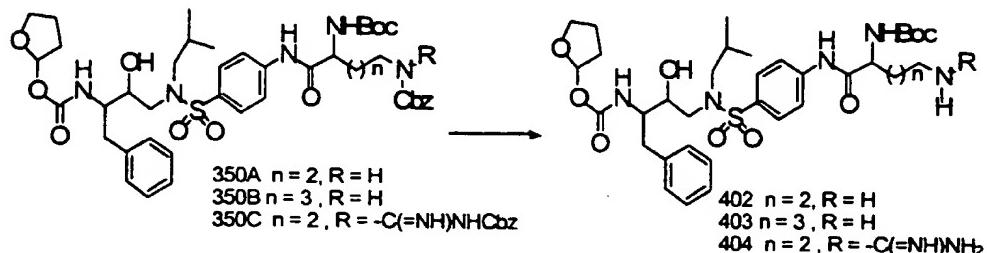
1H-NMR(CDCl₃): 0.85 (dd, 6H), 1.41 (s, 3H), 1.45 (s, 6H),
 1.60 (m, 4H), 1.90 (m, 2H), 2.1 (m, 1H), 2.75-3.25 (m,
 6H), 3.60-3.90 (m, 6H), 5.15 (dd, 2H), 7.2-7.4 (m, 10H),
 5 7.68 (dd, 4H).
 MS (ES-): 852 (M-1).
 MS (ES+): 854 (M+1).

Compound 350 B

10 1H-NMR(CDCl₃): 0.81 (dd, 6H), 1.39 (s, 9H), 1.40-2.10 (m,
 9H), 2.70-3.20 (m, 8H), 3.60-3.90 (m, 6H), 4.10 (m, 1H),
 4.80 (d, 1H), 5.04 (s(br), 2H), 7.1-7.3 (m, 10H), 7.61
 (s, 4H).
 MS (ES-): 866 (M-1).
 15 MS (ES+): 868 (M+1).

Compound 350 C

1H-NMR(CDCl₃): 0.86 (dd, 6H), 1.40 (s, 3H), 1.46 (s, 6H),
 1.60-2.10 (m, 7H), 2.70-3.15 (m, 6H), 3.60 (d, 1H), 3.70-
 20 4.10 (m, 6H), 4.81 (d, 1H), 5.05-5.30 (m, 7H), 7.18-7.4
 (m, 17H), 7.55 (d, 2H).
 MS (FAB+): 1030 (M+1), 1052 (M+Na).



25 Compounds 350A, 350B and 350C were converted to
 Compounds 402, 403, and 404, respectively, using the
 standard hydrogenation method set forth above:

H₂/PdC(10%), atmospheric pressure, 4 hours, room temperature, solvent: EtOH, Yield: 81 %.

Compound 402

5 ¹H-NMR(CDCl₃): 0.80 (dd, 6H), 1.38 (s, 9H), 1.8 (m, 6H), 2.10 (m, 2H), 2.75-3.30 (m, 8H), 3.50-4.00 (m, 7H), 4.55 (s(br), 1H), 7.2 (m, 5H), 7.60 (d, 2H), 7.81 (d, 2H).
MS (ES+): 720 (M+1).

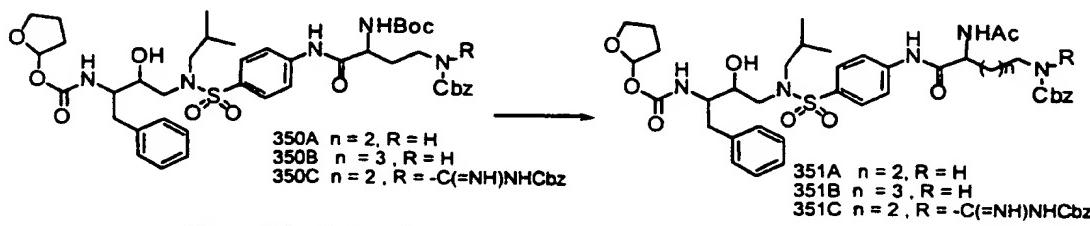
10 **Compound 403**

1H-NMR(CDCl₃): 0.87 (dd, 6H), 1.45 (s, 9H), 1.50-2.00 (m, 8H), 2.08 (m, 1H), 2.75-3.15 (m, 8H), 3.60 (d, 1H), 3.75-3.90 (m, 5H), 4.28 (s(br), 1H), 4.92 (d, 1H), 5.11 (m, 1H), 5.27 (s(br), 1H), 7.28-7.35 (m, 5H), 7.70 (s, 4H).
15 MS (ES+): 734 (M+1).

Compound 404

1H-NMR(CDCl₃): 0.80 (dd, 6H), 1.32 (s, 9H), 1.50-2.10 (m, 7H), 2.60-3.20 (m, 8H), 3.40-3.80 (m, 5H), 5.0 (s(br), 1H), 7.05-7.2 (m, 5H), 7.50-7.80 (m, 4H).
20 MS (ES+): 762 (M+1).

Example 47



25 We added 5 ml TFA to a stirred solution of 260 mg (0.3 mmol) Compound 350A, 350B, or 350C in 20 ml chloroform. The mixture was stirred for 5 hours at room temperature, and then the solvents were removed under

reduced pressure. The residue was dissolved in 20 ml dichloromethane, 2 ml (11 mmol) N,N-diisopropylethylamine and 1 ml (10 mmol) acetic anhydride was added to the reaction mixture. The solution was stirred for 1 hour, 5 then the solvents were removed. The residue was purified by silica gel chromatography (eluant: EtOAc-EtOH(9:1)) to obtain 170 mg (71 %) of compound 351A, 351B or 351C, respectively.

10 Compound 351A

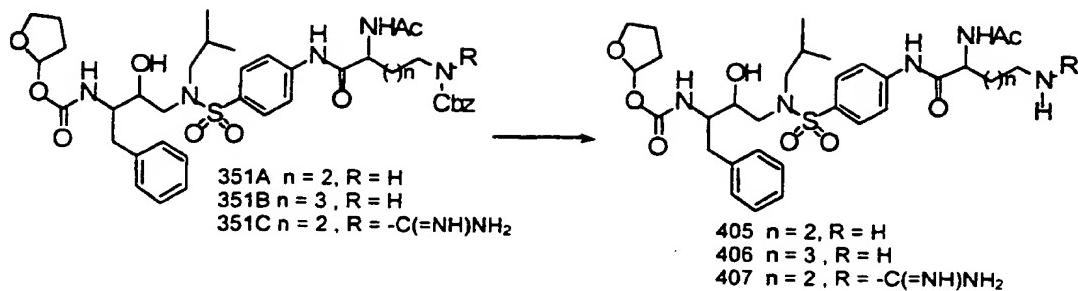
1H-NMR(CDCl₃): 0.85 (dd, 6H), 1.60 (m, 3H), 1.80-2.00 (m, 3H), 2.06 (2, 3H), 2.75 (dd, 1H), 2.80-3.20 (m, 5H), 3.60-3.90 (m, 7H), 4.85 (d, 2H), 5.10 (m, 3H), 6.46 (d, 1H), 7.25 (m, 10H), 7.67 (s, 4H), 9.30 (s, 1H).
15 MS (ES+): 796 (M+1), 818 (M+Na).

Compound 351B

1H-NMR(CDCl₃): 0.80 (dd, 6H), 1.38 (m, 2H), 1.50 (m, 2H), 1.70 (m, 2H), 1.85 (m, 2H), 2.00 (s, 3H), 2.70 (dd, 1H), 20 2.75-3.20 (m, 7H), 3.55 (d, 1H), 3.75 (m, 6H), 4.45 (q, 1H), 4.83 (d, 1H), 4.95 (t, 1H), 5.03 (s(br), 3H), 6.46 (d, 1H), 7.20 (m, 10H), 7.61 (s, 4H), 9.29 (s, 1H).
MS (ES+): 810 (M+1), 832 (M+Na).

25 Compound 351C

1H-NMR(CDCl₃): 0.85 (dd, 6H), 1.70-2.00 (m, 6H), 2.07 (s, 3H), 2.70 (dd, 1H), 2.80-3.00 (m, 3H), 3.10 (dd, 1H), 3.60 (d, 1H), 3.65-4.00 (m, 6H), 4.1(m, 1H), 4.62 (q, 1H), 4.82 (d, 1H), 5.00-5.30 (m, 5H), 7.10-7.40 (m, 30 15H), 7.55 (d, 2H), 7.65 (m, 3H) 9.18 (s(br), 1H), 9.45 (s(br), 1H), 9.56(s(br),1H).
MS (FAB+): 972 (M+1), 994 (M+Na).



The conversion of compounds 351A, 351C, and 351C to 405, 406, and 407, respectively was achieved by standard hydrogenation using H₂/PdC(10%), atmospheric pressure, 4 hours at room temperature, solvent: EtOH,
 Yield = 46%.

Compound 405

1H-NMR (DMSO-d₆): 0.85 (dd, 6H), 1.62 (m, 3H), 1.81 (m, 2H), 1.94 (s, 3H), 2.00-2.2 (m, 2H), 2.75-3.00 (m, 5H), 3.10 (m, 2H), 3.50-3.80 (m, 5H), 4.54 (m, 1H), 5.00 (m, 1H), 5.11 (d, 1H), 7.2-7.4 (m, 5H), 7.80-8.00 (m, 5H), 10.72 (s, 1H).
 MS (ES+): 662 (M+1).

15

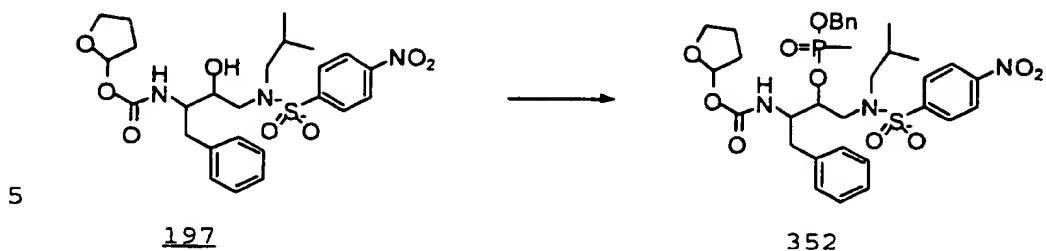
Compound 406

1H-NMR (DMSO-d₆): 0.80 (dd, 6H), 1.30-1.80 (m, 7H), 1.85 (s, 3H), 1.95-2.10 (m, 2H), 2.70 (m, 4H), 2.99 (m, 2H), 3.30 (m, 5H), 3.40-3.80 (m, 4H), 4.35 (m, 1H), 4.90 (s, 1H), 5.00 (d, 1H), 7.08-7.25 (m, 5H), 7.50 (s(br), 1H), 7.71 (d, 2H), 7.79 (d, 2H), 10.54 (s, 1H).
 MS (ES+): 676 (M+1).

Compound 407

25 1H-NMR (DMSO-d₆): 0.80 (dd, 6H), 1.40-1.60 (m, 4H), 1.75 (m, 2H), 1.86 (s, 3H), 2.00 (m, 2H), 2.75 (dt, 2H), 3.00 (m, 2H), 3.10 (q, 2H), 3.40-3.70 (m, 5H), 4.39 (q, 1H),

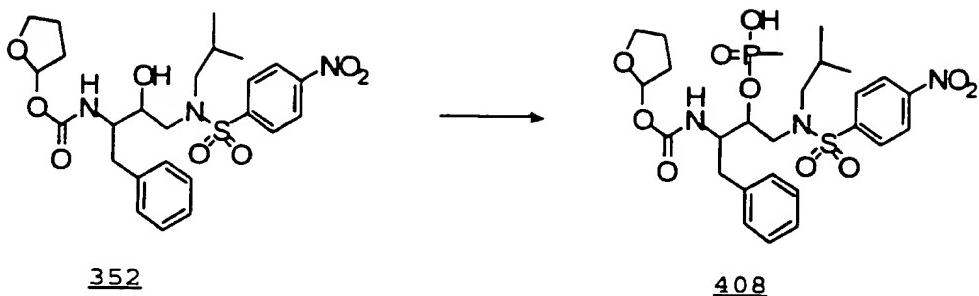
4.92 (s (br), 1H), 5.01 (d, 1H), 7.20 (m, 5H), 7.70 (d+m, 3H), 7.81 (d, 2H), 8.30 (d, 1H), 10.60 (s, 1H).
 MS (ES+): 704 (M+1).

Example 48

We added 1.0 g (7.5 mmol) methanephosphonyl dichloride to a stirred solution of 2.14 g (4.00 mmol) of compound 197 in 20 ml toluene, containing 10% pyridine. The mixture was stirred at 100°C for 5 hours, then cooled to 40°C, 2 g (18.5 mmol) benzyl alcohol was added to the reaction, and the mixture was stirred at 20°C for 12 hours. The solid was filtered, washed with 2 x 10 ml toluene and the filtrate was concentrated under reduced pressure. The residue was purified using silica gel chromatography (eluants: Hexane-EtOAc (1:1), then EtOAc (neat)) to yield 550 mg (20 %) of compound 352.

¹H-NMR (CDCl₃): 0.67 (dd, 6H), 1.53 (d, 3H), 1.70 (m, 1H), 1.90-2.10 (m, 2H), 2.65-3.20 (m, 6H), 3.55 (d, 1H), 3.80 (m, 3H), 4.10 (m, 1H), 4.70 (q, 1H), 4.90-5.20 (m, 4H), 6.37 (d, 1H), 7.2-7.4 (m, 10H), 7.90 (d, 2H), 8.30 (d, 2H).

MS (ES+): 704 (M+1), 726 (M+Na).



Compound 352 was converted to compound 408

5 using standard hydrogenation method: H₂/PdC(10%),
atmospheric pressure, 2 hours, room temperature, solvent:
MeOH; Yield: 78%.

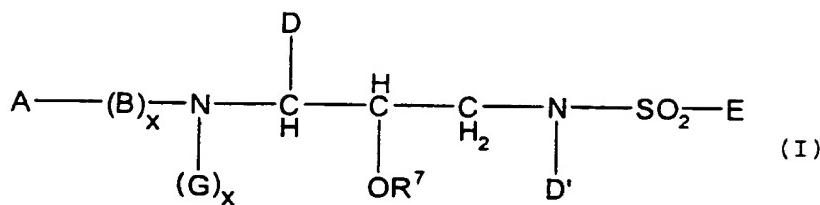
1H-NMR(DMSO-d₆): 0.84 (dd, 6H), 1.44 (d, 3H), 1.82 (m,
10 1H), 1.90-2.10 (m, 2H), 2.62 (m, 2H), 2.95 (m, 2H), 3.10
(d, 1H), 3.39 (d, 1H), 3.45-3.80 (m, 4H), 4.14 (t, 1H),
4.53 (m, 1H), 5.00 (s (br), 1H), 6.68 (d, 2H), 7.2-7.4
(m, 5H), 7.50 (d, 2H).
MS (ES-): 582 (M-1).

15 While we have described a number of embodiments of
this invention, it is apparent that our basic construc-
tions may be altered to provide other embodiments which
utilize the products and processes of this invention.
Therefore, it will be appreciated that the scope of this
20 invention is to be defined by the appended claims, rather
than by the specific embodiments which have been
presented by way of example.

CLAIMS

We claim:

1. A compound of formula I:



wherein:

A is selected from H; Ht; -R¹-Ht; -R¹-(C₁-C₆)-alkyl, which is optionally substituted with one or more groups independently selected from hydroxy, C₁-C₄ alkoxy, Ht, -O-Ht, -NR²-CO-N(R²)₂ or -CO-N(R²)₂; -R¹-(C₂-C₆)-alkenyl, which is optionally substituted with one or more groups independently selected from hydroxy, C₁-C₄ alkoxy, Ht, -O-Ht, -N(R²)-C(O)-N(R²)₂ or -CO-N(R²)₂; or R⁷;

each R¹ is independently selected from -C(O)-, -S(O)₂-, -C(O)-C(O)-, -O-C(O)-, -O-S(O)₂, -N(R²)-S(O)₂-, -N(R²)-(O)- or -N(R²)-C(O)-C(O)-;

each Ht is independently selected from C₃-C₇ cycloalkyl; C₅-C₇ cycloalkenyl; C₆-C₁₀ aryl; or a 5-7 membered saturated or unsaturated heterocycle, containing one or more heteroatoms selected from N, N(R²), O, S and S(O)_n; wherein said aryl or said heterocycle is optionally fused to Q; and wherein any member of said Ht is optionally substituted with one or more substituents independently selected from oxo, -OR², SR², -R², -N(R²)₂, -R²-OH, -CN, -C(O)O-R², -C(O)-N(R²)₂, -S(O)₂-N(R²)₂, -N(R²)-C(O)-R², -C(O)-R², -S(O)_n-R², -OCF₃, -S(O)_n-Q, methylenedioxy, -N(R²)-S(O)₂-R², halo, -CF₃, -NO₂, Q, -OQ, -OR⁷, -SR⁷, -R⁷, -N(R²)(R⁷) or -N(R⁷)₂;

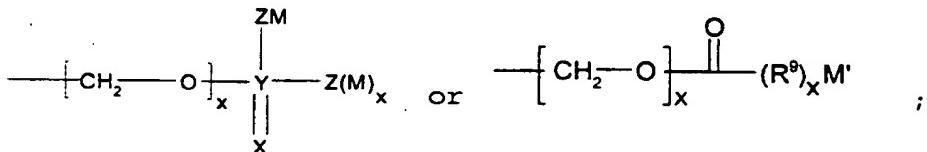
each R² is independently selected from H, or (C₁-C₄)-alkyl optionally substituted with Q;
B, when present, is -N(R²)-C(R³)₂-C(O)-;
each x is independently 0 or 1;
each R³ is independently selected from H, Ht, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₃-C₆)-cycloalkyl or (C₅-C₆)-cycloalkenyl; wherein any member of said R³, except H, is optionally substituted with one or more substituents selected from -OR², -C(O)-NH-R², -S(O)_n-N(R²)₂, Ht, -CN, -SR², -CO₂R², N(R²)-C(O)-R²;
each n is independently 1 or 2;
G, when present, is selected from H, R⁷ or (C₁-C₄)-alkyl, or, when G is (C₁-C₄)-alkyl, G and R⁷ are bound to one another either directly or through a C₁-C₃ linker to form a heterocyclic ring; or when G is absent, the atom to which G is attached is bound directly to the R⁷ group in -OR⁷ with the concomitant displacement of one -ZM group from R⁷;
D and D' are independently selected from Q; (C₁-C₆)-alkyl, which is optionally substituted with one or more groups selected from (C₃-C₆)-cycloalkyl, -OR², -R³, -O-Q or Q; (C₂-C₄)-alkenyl, which is optionally substituted with one or more groups selected from (C₃-C₆)-cycloalkyl, -OR², -R³, -O-Q or Q; (C₃-C₆)-cycloalkyl, which is optionally substituted with or fused to Q; or (C₅-C₆)-cycloalkenyl, which is optionally substituted with or fused to Q;
each Q is independently selected from a 3-7 membered saturated, partially saturated or unsaturated carbocyclic ring system; or a 5-7 membered saturated, partially saturated or unsaturated heterocyclic ring containing one or more heteroatoms selected from O, N, S,

$S(O)_n$ or $N(R^2)$; wherein any ring in Q is optionally substituted with one or more groups selected from oxo, $-OR^2$, $-R^2$, $-N(R^2)_2$, $-N(R^2)-C(O)-R^2$, $-R^2-OH$, $-CN$, $-C(O)OR^2$, $-C(O)-N(R^2)_2$, halo or $-CF_3$;

E is selected from Ht; $O-Ht$; $Ht-Ht$; $-O-R^3$; $-N(R^2)(R^3)$; (C_1-C_6)-alkyl, which is optionally substituted with one or more groups selected from R^4 or Ht; (C_2-C_6)-alkenyl, which is optionally substituted with one or more groups selected from R^4 or Ht; (C_3-C_6)-saturated carbocycle, which is optionally substituted with one or more groups selected from R^4 or Ht; or (C_5-C_6)-unsaturated carbocycle, which is optionally substituted with one or more groups selected from R^4 or Ht;

each R^4 is independently selected from $-OR^2$, $-SR^2$, $-C(O)-NHR^2$, $-S(O)_2-NHR^2$, halo, $-N(R^2)-C(O)-R^2$, $-N(R^2)_2$ or $-CN$;

each R^7 is independently selected from



wherein each M is independently selected from H, Li, Na, K, Mg, Ca, Ba, $-N(R^2)_4$, (C_1-C_{12})-alkyl, (C_2-C_{12})-alkenyl, or $-R^6$; wherein 1 to 4 $-\text{CH}_2$ radicals of the alkyl or alkenyl group, other than the $-\text{CH}_2$ that is bound to Z, is optionally replaced by a heteroatom group selected from O, S, $S(O)$, $S(O)_2$, or $N(R^2)$; and wherein any hydrogen in said alkyl, alkenyl or R^6 is optionally replaced with a substituent selected from oxo, $-OR^2$, $-R^2$, $N(R^2)_2$, $N(R^2)_3$, R^2OH , $-CN$, $-C(O)OR^2$, $-C(O)-N(R^2)_2$, $S(O)_2-N(R^2)_2$, $N(R^2)-C(O)-R_2$, $C(O)R^2$, $-S(O)_n-R^2$, OCF_3 , $-S(O)_n-R^6$, $N(R^2)-S(O)_2-R^2$, halo, $-CF_3$, or $-NO_2$;

M' is H, (C₁-C₁₂)-alkyl, (C₂-C₁₂)-alkenyl, or -R⁶; wherein 1 to 4 -CH₂ radicals of the alkyl or alkenyl group is optionally replaced by a heteroatom group selected from O, S, S(O), S(O)₂, or N(R²); and wherein any hydrogen in said alkyl, alkenyl or R⁶ is optionally replaced with a substituent selected from oxo, -OR², -R², -N(R²)₂, N(R²)₃, -R²OH, -CN, -CO₂R², -C(O)-N(R²)₂, -S(O)₂-N(R²)₂, -N(R²)-C(O)-R₂, -C(O)R², -S(O)_n-R², -OCF₃, -S(O)_n-R⁶, -N(R²)-S(O)₂-R², halo, -CF₃, or -NO₂;

Z is CH₃, O, S, N(R²)₂, or, when M is not present, H.

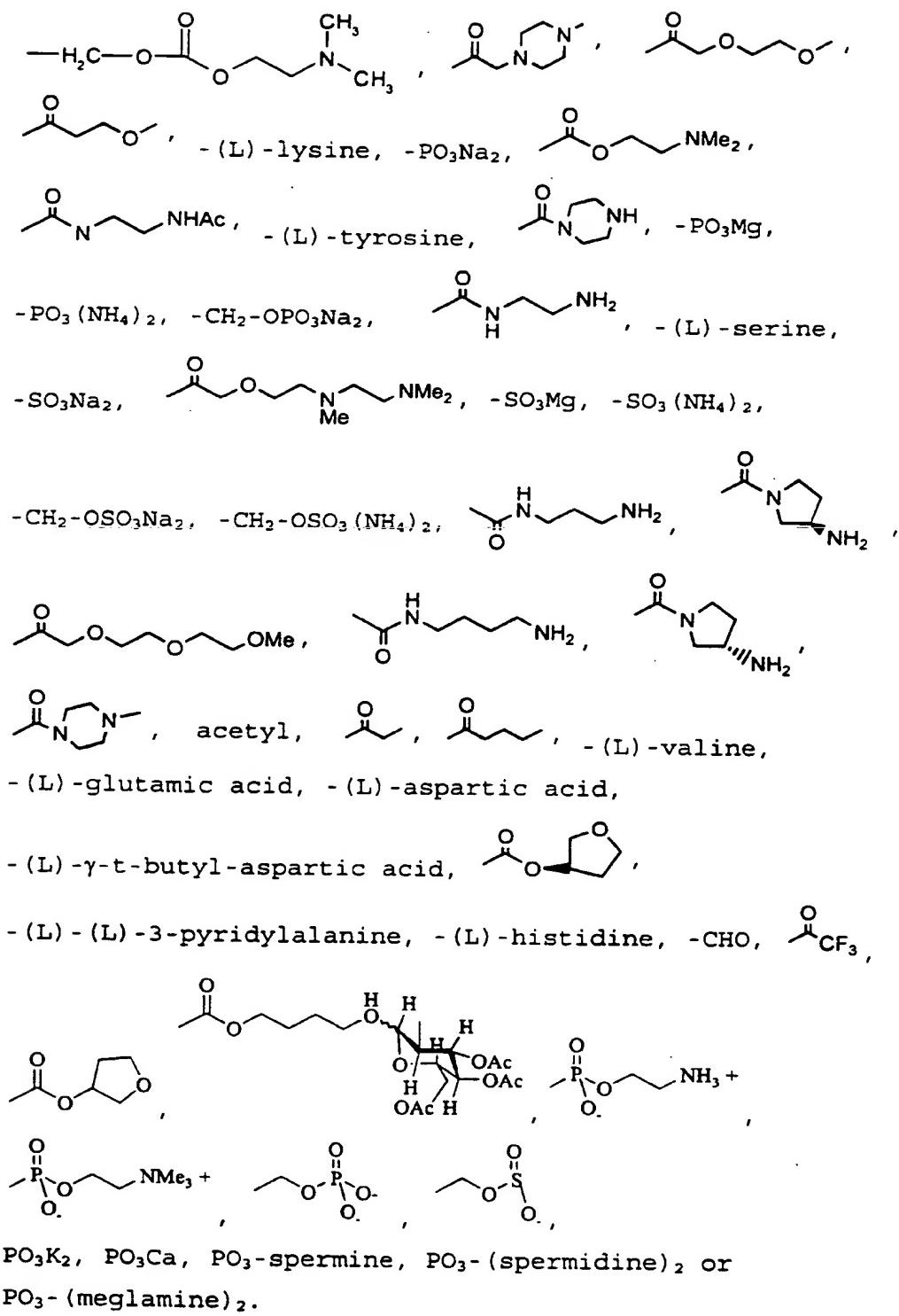
Y is P or S;

X is O or S; and

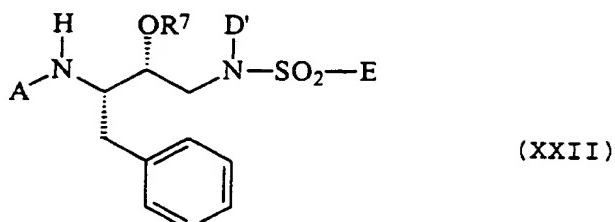
R⁹ is C(R²)₂, O or N(R²); and wherein when Y is S, Z is not S; and

R⁶ is a 5-6 membered saturated, partially saturated or unsaturated carbocyclic or heterocyclic ring system, or an 8-10 membered saturated, partially saturated or unsaturated bicyclic ring system; wherein any of said heterocyclic ring systems contains one or more heteroatoms selected from O, N, S, S(O)_n or N(R²); and wherein any of said ring systems optionally contains 1 to 4 substituents independently selected from OH, C₁-C₄ alkyl, O-(C₁-C₄)-alkyl or O-C(O)-(C₁-C₄)-alkyl.

2. The compound according to claim 1, wherein at least one R⁷ is selected from:



3. The compound according to claim 2, wherein said compound has formula XXII:



wherein A, D', R⁷ and E are as defined in claim 1.

4. The compound according to claim 3, wherein A is selected from 3-tetrahydrofuryl-O-C(O)-, 3-(1,5-dioxane)-O-C(O)-, or 3-hydroxy-hexahydrofura[2,3-b]-furanyl-O-C(O)-;

D' is (C₁-C₄)-alkyl which is optionally substituted with one or more groups selected from the group consisting of (C₃-C₆)-cycloalkyl, -OR², -R³, -O-Q and Q;

E is (C₆-C₁₀)-aryl optionally substituted with one or more substituents selected from oxo, -OR², SR², -R², -N(R²)₂, -R²-OH, -CN, -C(O)O-R², -C(O)-N(R²)₂, -S(O)₂-N(R²)₂, -N(R²)-C(O)-R², -C(O)-R², -S(O)_n-R², -OCF₃, -S(O)_n-Q, methylenedioxy, -N(R²)-S(O)₂-R², halo, -CF₃, -NO₂, Q, -OQ, -OR⁷, -SR⁷, -R⁷, -N(R²)(R⁷) or -N(R⁷)₂; or a 5-membered heterocyclic ring containing one S and optionally containing N as an additional heteroatom, wherein said heterocyclic ring is optionally substituted with one to two groups independently selected from -CH₃, R⁴, or Ht; and

Ht, insofar as it is defined as part of R³, is defined as in claim 1 except for the exclusion of heterocycles.

5. The compound according to claim 4,
wherein:

A is 3-tetrahydrofuryl-O-C(O)-;
G is hydrogen;
D' is isobutyl;
E is phenyl substituted with N(R⁷)₂;
each M is independently selected from H, Li, Na, K,
Mg, Ca, Ba, C₁-C₄ alkyl or -N(R²)₄; and
each M' is H or C₁-C₄ alkyl.

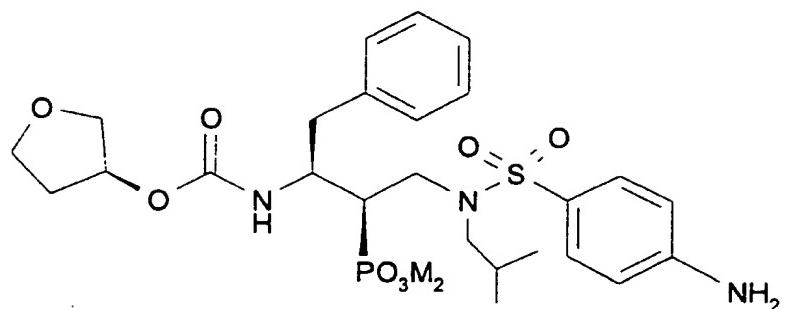
6. The compound according to claim 3,
wherein:

E is a 5-membered heterocyclic ring containing one S
and optionally containing N as an additional heteroatom,
wherein said heterocyclic ring is optionally substituted
with one to two groups independently selected from -CH₃,
R⁴, or Ht.

7. The compound according to claim 3,
wherein:

E is Ht substituted with N(R⁷)₂;
R⁷ in the -OR⁷ group shown in formula XXII is
-PO(OM)₂ or C(O)CH₂CH₂OCH₂CH₂OCH₃, and both R⁷ in the
-N(R⁷)₂ substituent of Ht are H; or R⁷ in -OR⁷ group shown
in formula XXII is C(O)CH₂CH₂OCH₃, one R⁷ in the -N(R⁷)₂
substituent of Ht is C(O)CH₂CH₂OCH₃ and the other R⁷ in
the -N(R⁷)₂ substituent of Ht is H; and
wherein M is H, Li, Na, K or C₁-C₄ alkyl.

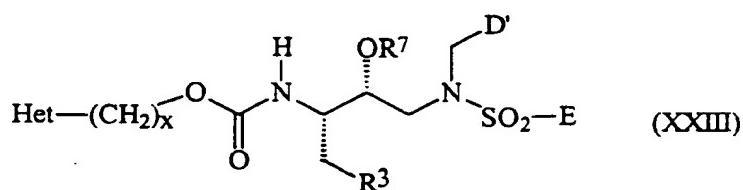
8. The compound according to claim 3, having the structure:



wherein each M is Na or K.

9. The compound according to claim 8, wherein each M is Na.

10. The compound according to claim 2, wherein said compound has formula XXIII:



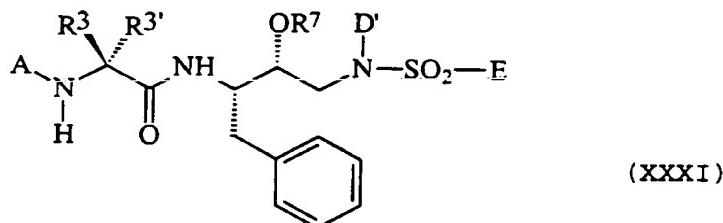
11. The compound according to claim 10, wherein:

R^3 is (C_1-C_6) -alkyl, (C_2-C_6) -alkenyl, (C_5-C_6) -cycloalkyl, (C_5-C_6) -cycloalkenyl, or a 5-6 membered saturated or unsaturated heterocycle; wherein any member of R^3 is optionally substituted with one or more substituents selected from the group consisting of $-\text{OR}^2$, $-\text{C}(\text{O})-\text{NH}-\text{R}^2$, $-\text{S}(\text{O})_n\text{N}(\text{R}^2)_2$, $-\text{Ht}$, $-\text{CN}$, $-\text{SR}^2$, $-\text{C}(\text{O})\text{O}-\text{R}^2$ and $\text{N}(\text{R}^2)-\text{C}(\text{O})-\text{R}^2$; and

D' is (C₁-C₃)-alkyl or C₃ alkenyl; wherein D' is optionally substituted with one or more groups selected from (C₃-C₆)-cycloalkyl, -OR², -O-Q or Q.

12. The compound according to claim 11, wherein R⁷ in the -OR⁷ group depicted in formula XXIII is -PO(OM)₂ or -C(O)-M'.

13. The compound according to claim 2, wherein said compound has formula XXXI:



14. The compound according to claim 13, wherein:

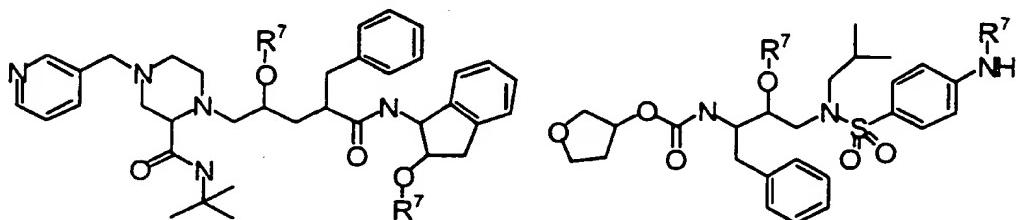
A is R¹-Ht;

each R³ is independently (C₁-C₆)-alkyl which is optionally substituted with -OR², -C(O)-NH-R², -S(O)_nN(R²)₂, -Ht, -CN, -SR², -CO₂R² or -N(R²)-C(O)-R²; and D' is (C₁-C₄)-alkyl, which is optionally substituted with (C₃-C₆)-cycloalkyl, -OR², -O-Q; and E is Ht, Ht-Ht and -N(R²)(R³).

15. The compound according to claim 14, wherein R⁷ in the -OR⁷ group depicted in formula XXXI is -PO(OM)₂ or -C(O)-M'.

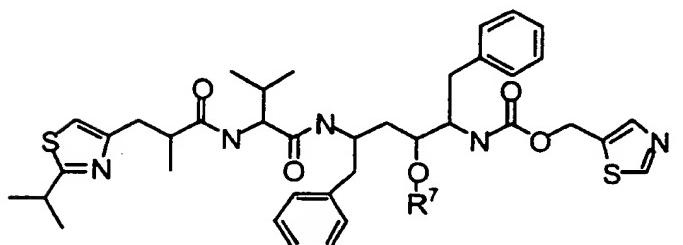
16. The compound according to claim 1, wherein said compound is selected from any one of compound numbers 198 to 231, 237 to 242, 245 to 267, or 308, depicted in Table 1; any one of compound numbers 232 to 236 depicted in Table II; or any one of compound numbers 243 to 244 depicted in Table III.

17. A compound selected from:

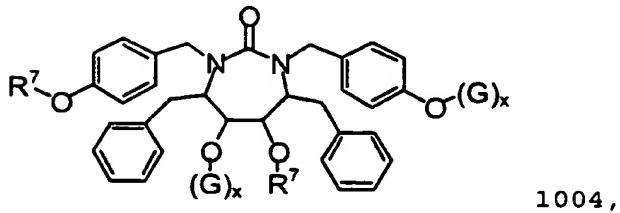


1001

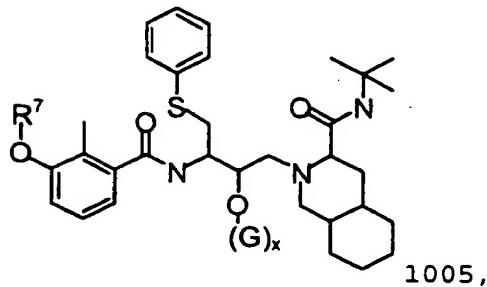
1002



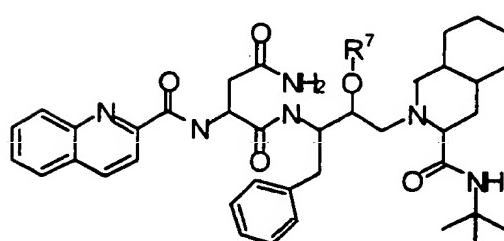
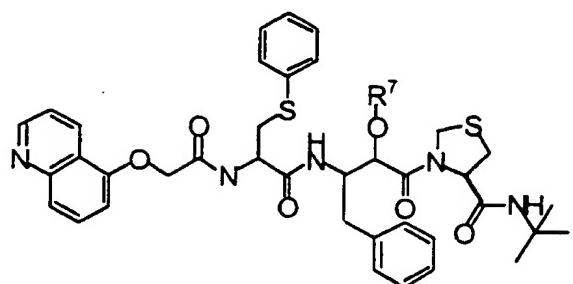
1003,



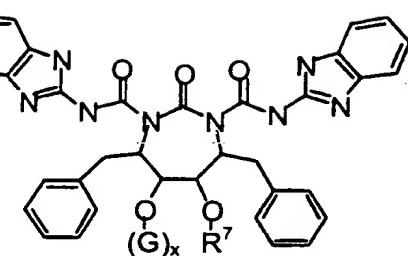
1004,



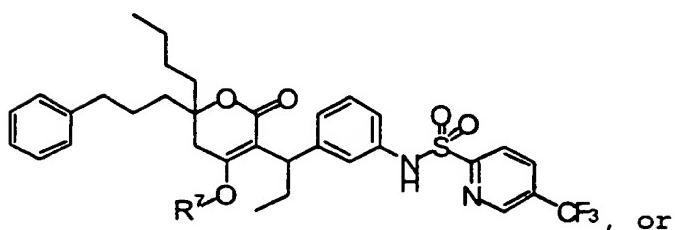
1005,



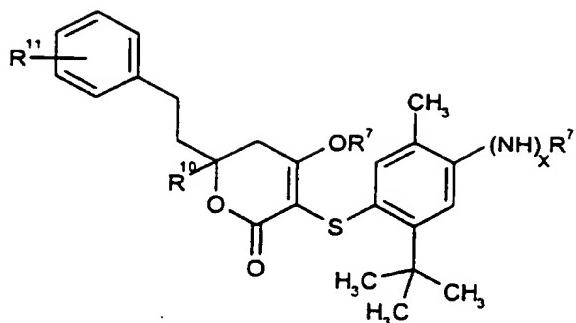
1007



1008



1009



wherein:

R^{10} is selected from isopropoyl or cyclopentyl;

R^{11} is selected from NHR^7 or OR^7 ;

in compound 1005, when R^7 is PO_3M , $(G)_x$ is not H; and x , R^7 and G are as defined in claim 1.

18. A pharmaceutical composition, comprising a compound according to any one of claims 1 to 17 in an amount effective to treat infection by a virus that is characterized by an aspartyl protease; and a pharmaceutically acceptable carrier, adjuvant or vehicle.

19. The pharmaceutical composition according to claim 18, wherein said virus is HIV.

20. The pharmaceutical composition according to claim 18, wherein said pharmaceutical composition is formulated for oral administration.

21. The pharmaceutical composition according to claim 18, further comprising one or more agents selected from an anti-viral agent, an HIV protease inhibitor other than a compound according to claim 1, and an immunostimulator.

22. The pharmaceutical composition according to claim 21, further comprising one or more agents selected from zidovudine (AZT), zalcitabine (ddC), didanosine (ddI), stavudine (d4T), 3TC, 935U83, 1592U89, 524W91, saquinavir (Ro 31-8959), L-735,524, SC-52151, ABT 538 (A80538), AG 1341, XM 412, XM 450, CPG 53,437, or tuscarasol.

23. A method for inhibiting aspartyl protease activity in a mammal, comprising the step of contacting administering to said mammal a pharmaceutical composition according to claim 18.

24. A method for treating HIV infection in a mammal comprising the step of administering to said mammal a pharmaceutical composition according to any one of claim 18.

25. The method according to claim 24, wherein said mammal is additionally administered one or more additional agents selected from an anti-viral agent, an HIV protease inhibitor other than a compound according to claim 1, and an immunostimulator either as a part of a single dosage form with said pharmaceutical composition or as a separate dosage form.

26. The method according to claim 25, wherein said additional agent is selected from zidovudine (AZT), zalcitabine (ddC), didanosine (ddI), stavudine (d4T), 3TC, 935U83, 1592U89, 524W91, saquinavir (Ro 31-8959), L-

735,524, SC-52151, ABT 538 (A80538), AG 1341, XM 412, XM 450, CPG 53,437, or tuscarasol.

27. The method according to claim 24, wherein said step of administering comprises oral administration.

INTERNATIONAL SEARCH REPORT

Inte
nal Application No
PCT/US 98/04595

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D307/20 A61K31/34 A61K31/66 A61K31/665 A61K31/70
 A61K31/16 C07D405/12 C07C311/18 C07H15/18 C07F9/655
 C07F9/6584

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D C07C C07H C07F A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>WO 94 05639 A (MURCKO MARK A ; VERTEX PHARMA (US); TUNG ROGER D (US); BHISETTI GOV) 17 March 1994 cited in the application see abstract; claims 1,9; example 168 see page 55 see page 68, line 10 - line 12 see page 79, line 7 - line 16</p> <p>-----</p>	1-27

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

27 August 1998

Date of mailing of the international search report

21/09/1998

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.
 Fax: (+31-70) 340-3016

Authorized officer

Paisdor, B

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 98/04595**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: **23-27**
because they relate to subject matter not required to be searched by this Authority, namely:
**Remark: Although claims 23-27
are directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.**
2. Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte. Application No.

PCT/US 98/04595

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9405639	A 17-03-1994	AP 390 A	02-08-1995
		AU 691160 B	14-05-1998
		AU 4852093 A	29-03-1994
		BG 99540 A	30-11-1995
		CA 2143208 A	17-03-1994
		CN 1087347 A	01-06-1994
		CZ 9500587 A	13-12-1995
		EP 0659181 A	28-06-1995
		FI 951059 A	18-04-1995
		HU 71892 A	28-02-1996
		JP 8501299 T	13-02-1996
		LT 917 A,B	25-11-1994
		NO 950876 A	08-05-1995
		NZ 256238 A	24-04-1997
		PL 307858 A	26-06-1995
		SG 43862 A	14-11-1997
		SK 29395 A	13-09-1995
		US 5585397 A	17-12-1996
		US 5783701 A	21-07-1998
		US 5723490 A	03-03-1998